Department of Biotechnology and Biomedicine - DTU Orbit (17/06/2018)

Department of Biotechnology and Biomedicine

Technical University of Denmark
Short name: DTU Bioengineering

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Organisation profile
Head of Department: Bjarke Bak Christensen
The department addresses important social and scientific challenges within biotechnology, biomedicine, food technology and human health. The department engages in both basic research and applied research and employs a number of basic tools from biochemistry, biophysics, chemistry, cell biology, immunology, microbial ecology and physiology, bioinformatics, and bioengineering. DTU Bioengineering has four research platforms that provide state-of-the-art research within fermentation and high-throughput screening, metabolomics-based mass spectrometry, proteomics, and genomics.

Organisational unit: Department

Publications:

Linking secondary metabolites to gene clusters through genome sequencing of six diverse Aspergillus species
The fungal genus of Aspergillus is highly interesting, containing everything from industrial cell factories, model organisms, and human pathogens. In particular, this group has a prolific production of bioactive secondary metabolites (SMs). In this work, four diverse Aspergillus species (A. campestris, A. novofumigatus, A. ochraceoroseus, and A. steynii) have been whole-genome PacBio sequenced to provide genetic references in three Aspergillus sections. A. taichungensis and A. candidus also were sequenced for SM elucidation. Thirteen Aspergillus genomes were analyzed with comparative genomics to determine phylogeny and genetic diversity, showing that each presented genome contains 15–27% genes not found in other sequenced Aspergillus. In particular, A. novofumigatus was compared with the pathogenic species A. fumigatus. This suggests that A. novofumigatus can produce most of the same allergens, virulence, and pathogenicity factors as A. fumigatus, suggesting that A. novofumigatus could be as pathogenic as A. fumigatus. Furthermore, SMs were linked to gene clusters based on biological and chemical knowledge and analysis, genome sequences, and predictive algorithms. We thus identify putative SM clusters for aflatoxin, chlorflavonin, and ochrindol in A. ochraceoroseus, A. campestris, and A. steynii, respectively, and novofumigatoin, ent-cycloechinulin, and episazonalenins in A. novofumigatus. Our study delivers six fungal genomes, showing the large diversity found in the Aspergillus genus; highlights the potential for discovery of beneficial or harmful SMs; and supports reports of A. novofumigatus pathogenicity. It also shows how biological, biochemical, and genomic information can be combined to identify genes involved in the biosynthesis of specific SMs.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Fungal Chemodiversity, Natural Product Discovery, Department of Biotechnology, Eukaryotic Molecular Cell Biology, U.S. Department of Energy, University of Manchester
Accelerated collagen turnover in women with angina pectoris without obstructive coronary artery disease: An iPOWER substudy

Aim: Collagens are major cardiac extracellular matrix components, known to be actively remodelled and accumulated during diffuse myocardial fibrosis. We evaluated whether accelerated collagen turnover described by neo-epitope biomarkers reflecting collagen formation and degradation separates patients with diffuse myocardial fibrosis from asymptomatic controls.

Methods and results: Seventy-one women with angina pectoris without significant coronary artery disease assessed by invasive coronary angiogram were included. Competitive enzyme-linked immunosorbent assays (ELISAs) measuring circulating protein fragments in serum assessed the formation and degradation of collagen type III (Pro-C3, C3M and C3C), IV (P4NP7S and C4M), V (Pro-C5 and C5M) and VI (Pro-C6 and C6M), and degradation of collagen type I (C1M). Serum samples from 32 age-matched asymptomatic women were included as controls. Symptomatic women presented significantly elevated levels of Pro-C6, C3C, C3M, C4M and C8-C (p < 0.0001–0.0058) and significantly decreased levels of Pro-C3, C5M and C6M (p < 0.0001–0.041), reflecting accelerated collagen turnover and an imbalanced collagen formation and degradation compared to controls. Cardiac magnetic resonance T1 mapping was performed to determine extracellular volume fraction and thus diffuse myocardial fibrosis. A significant association was identified between C5M and extracellular volume fraction by cardiac magnetic resonance (p = 0.01).

Conclusion: Women with angina pectoris, but without significant obstructive coronary artery disease, showed an imbalanced collagen turnover compared to asymptomatic controls. The examined biomarkers are tools to monitor active collagen remodelling in patients with angina pectoris, in risk of developing myocardial fibrosis.

General information
State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Bio and Health Informatics, University of Copenhagen, Nordic Bioscience A/S, ProScion A/S
Authors: Nielsen, S. H. (Intern), Mygind, N. D. (Ekstern), Michelsen, M. M. (Ekstern), Bechsgaard, D. F. (Ekstern), Suhrs, H. E. (Ekstern), Genovese, F. (Ekstern), Nielsen, H. B. (Ekstern), Brix, S. (Intern), Karsdal, M. (Ekstern), Prescott, E. (Ekstern), Kastrup, J. (Ekstern)
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BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 1.545 SJR 2.037
BFI (2016): BFI-level 2
Scopus rating (2016): SNIP 1.194 SJR 1.634 CiteScore 2.94
A comprehensive and quantitative comparison of text-mining in 15 million full-text articles versus their corresponding abstracts

Across academia and industry, text mining has become a popular strategy for keeping up with the rapid growth of the scientific literature. Text mining of the scientific literature has mostly been carried out on collections of abstracts, due to their availability. Here we present an analysis of 15 million English scientific full-text articles published during the period 1823-2016. We describe the development in article length and publication sub-topics during these nearly 250 years. We showcase the potential of text mining by extracting published protein-protein, disease-gene, and protein subcellular associations using a named entity recognition system, and quantitatively report on their accuracy using gold standard benchmark data sets. We subsequently compare the findings to corresponding results obtained on 16.5 million abstracts included in MEDLINE and show that text mining of full-text articles consistently outperforms using abstracts only.
A critical review of producers of small lactone mycotoxins: patulin, penicillic acid and moniliformin

A very large number of filamentous fungi has been reported to produce the small lactone mycotoxins patulin, penicillic acid and moniliformin. Among the 167 reported fungal producers of patulin, only production by 29 species could be confirmed. Patulin is produced by 3 Aspergillus species, 3 Paecilomyces species, 22 Penicillium species from 7 sections of Penicillium, and one Xylaria species. Among 101 reported producers of penicillic acid, 48 species could produce this mycotoxin. Penicillic acid is produced by 23 species in section Aspergillus subgenus Circumdati section Circumdati, by Malbranchea aurantiaca and by 24 Penicillium species from 9 sections in Penicillium and one species that does not actually belong to Penicillium (P. megasporum). Among 40 reported producers of moniliformin, five species have been regarded as doubtful producers of this mycotoxin or are now regarded as taxonomic synonyms. Moniliformin is produced by 34 Fusarium species and one Penicillium species. All the accepted producers of patulin, penicillic acid and moniliformin were revised according to the new one fungus -one name nomenclatural system, and the most recently accepted taxonomy of the species.
The extracellular matrix (ECM) plays a vital role in maintaining normal tissue function. Collagens are major components of the ECM and there is a tight equilibrium between degradation and formation of these proteins ensuring tissue health and homeostasis. As a consequence of tissue turnover, small collagen fragments are released into the circulation, which act as important biomarkers in the study of certain tissue-related remodeling factors in health and disease. The aim of this study was to establish an age-related collagen turnover profile of the main collagens of the interstitial matrix (type I and III collagen) and basement membrane (type IV collagen) in healthy men and women. By using well-characterized competitive ELISA-assays, we assessed specific fragments of degraded (C1M, C3M, C4M) and formed (PINP, Pro-C3, P4NP7S) type I, III and IV collagen in serum from 617 healthy men and women ranging in ages from 22 to 86. Subjects were divided into 5-year age groups according to their sex and age. Groups were compared using Kruskal-Wallis adjusted for Dunn's
multiple comparisons test and Mann-Whitney t-test. Age-specific changes in collagen turnover was most profound for type I collagen. PINP levels decreased in men with advancing age, whereas in women, the level decreased in early adulthood followed by an increase around the age of menopause (age 40-60). Sex-specific changes in type I, III and IV collagen turnover was present at the age around menopause (age 40-60) with women having an increased turnover. In summary, collagen turnover is affected by age and sex with the interstitial matrix and the basement membrane being differently regulated. The observed changes needs to be accounted for when measuring ECM related biomarkers in clinical studies.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Bio and Health Informatics, Nordic Bioscience A/S, Charité-Universitätsmedizin Berlin
Authors: Kehlet, S. N. (Intern), Willumsen, N. (Ekstern), Armbrecht, G. (Ekstern), Dietzel, R. (Ekstern), Brix, S. (Intern), Henriksen, K. (Ekstern), Karsdal, M. A. (Ekstern)
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Scopus rating (2017): SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.425 SNIP 1.233 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.705 SNIP 1.178
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.614 SNIP 1.046
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.506 SNIP 1.006
Web of Science (2008): Indexed yes
Aggrecanase degradation of type III collagen is associated with clinical knee pain

There is a lack of biochemical markers for non-invasive and objective assessment of symptomatic osteoarthritis (OA). Aggrecanase activity has been shown to be associated with joint deterioration and symptomatic disease through the degradation of extracellular matrix proteins, such as type III collagen. Our study aimed to identify and develop a novel biomarker by measuring an aggrecanase-mediated type III collagen neoepitope, and correlate levels of this biomarker with OA joint pain. Mass spectrometric analysis of purified type III collagen, degraded by the aggrecanase A Disintegrin and Metalloproteinase with Thrombospondin motif (ADAMTS), revealed a fragment generated by ADAMTS-1, -4 and -8. A monoclonal antibody was raised against the neoepitope of this fragment (COL3-ADAMTS) and a competitive ELISA was developed and tested; using serum samples from a cross-sectional cohort of patients with different degrees of knee OA (n=261). The COL3/ADAMTS ELISA was technically robust and specific for the ADAMTS-1, -4 and -8 generated neoepitope. COL3/ADAMTS was released from cytokine stimulated synovial cultures, indicating a biologic link between the marker and synovium. In OA patients, serum COL3/ADAMTS was independently associated with pain scores (rho=-0.13-0.17, p< 0.05). This association was associated significantly with the presence of radiographic OA. Together, these data indicate that COL3/ADAMTS could be a marker of early osteoarthritis and the underlying pathology.
Analysis of a gene panel for targeted sequencing of colorectal cancer samples

Colorectal cancer (CRC) is a leading cause of death worldwide. Surgical intervention is a successful treatment for stage I patients, whereas other more advanced cases may require adjuvant chemotherapy. The selection of effective adjuvant treatments remains, however, challenging. Accurate patient stratification is necessary for the identification of the subset of patients likely responding to treatment, while sparing others from pernicious treatment. Targeted sequencing approaches may help in this regard, enabling rapid genetic investigation, and at the same time easily applicable in routine diagnosis.

We propose a set of guidelines for the identification, including variant calling and filtering, of somatic mutations driving tumorigenesis in the absence of matched healthy tissue. We also discuss the inclusion criteria for the generation of our gene panel. Furthermore, we evaluate the prognostic impact of individual genes, using Cox regression models in the context of overall survival and disease-free survival. These analyses confirmed the role of commonly used biomarkers, and shed light on controversial genes such as CYP2C8.

Applying those guidelines, we created a novel gene panel to investigate the onset and progression of CRC in 273 patients. Our comprehensive biomarker set includes 266 genes that may play a role in the progression through the different stages of the disease. Tracing the developmental state of the tumour, and its resistances, is instrumental in patient stratification and reliable decision making in precision clinical practice.

General information
State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Integrative Systems Biology, Department of Systems Biology, Intomics A/S, Vejle Hospital, Exiqon A/S
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Main Research Area: Technical/natural sciences
An electroplated copper–silver alloy as antibacterial coating on stainless steel

Transfer and growth of pathogenic microorganisms must be prevented in many areas such as the clinical sector. One element of transfer is the adhesion of pathogens to different surfaces and the purpose of the present study was to develop and investigate the antibacterial efficacy of stainless steel electroplated with a copper-silver alloy with the aim of developing antibacterial surfaces for the medical and health care sector. The microstructural characterization showed a porous microstructure of electroplated copper-silver coating and a homogeneous alloy with presence of interstitial silver. The copper-silver alloy coating showed active corrosion behavior in chloride-containing environments. ICP-MS measurements revealed a selective and localized dissolution of copper ions in wet conditions due to its galvanic coupling with silver. No live bacteria adhered to the copper-silver surfaces when exposed to suspensions of S. aureus and E. coli at a level of 10^8 CFU/ml whereas 10^4 CFU/cm² adhered after 24h on the stainless steel controls. In addition, the Cu-Ag alloy caused a significant reduction of bacteria in the suspensions. The coating was superior in its antibacterial activity as compared to pure copper and silver electroplated surfaces. Therefore, the results showed that the electroplated copper-silver coating represents an effective and potentially economically feasible way of limiting surface spreading of pathogens.
Original language: English
Copper, Silver, Electroplating, Coating, Antibacterial

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An Online Compendium of CHO RNA-Seq Data Allows Identification of CHO Cell Line-specific Transcriptomic Signatures

Chinese hamster ovary (CHO) cell lines can fold, assemble and modify proteins post-translationally to produce human-like proteins; as a consequence, it is the single most common expression systems for industrial production of recombinant therapeutic proteins. A thorough knowledge of cultivation conditions of different CHO cell lines has been developed over the last decade, but comprehending gene or pathway-specific distinctions between CHO cell lines at transcriptome level remains a challenge. To address these challenges, we compiled a compendium of 23 RNA-Seq studies from public and in-house data on CHO cell lines, i.e. CHO-S, CHO-K1 and DG44. Significantly differentially expressed (DE) genes particularly related to subcellular structure and macromolecular categories were used to identify differences between the cell lines. A R-based web application was developed specifically for CHO cell lines to further visualize expression values across different cell lines, and make available the normalized full CHO data set graphically as a CHO research community resource. This study quantitatively categorizes CHO cell lines based on patterns at transcriptomic level and detects gene and pathway specific key distinctions among sibling cell lines. Studies such as this can be used to select desired characteristics across various CHO cell lines. Furthermore, the availability of the data as an internet-based application can be applied to broad range of CHO engineering applications.

General information
State: Accepted/In press
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Singh, A. (Intern), Kildegaard, H. F. (Intern), Andersen, M. R. (Intern)
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Main Research Area: Technical/natural sciences

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Scopus rating (2016): CiteScore 3.2 SJR 1.29 SNIP 0.969
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.172 SNIP 0.874 CiteScore 2.91
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.189 SNIP 1.062 CiteScore 2.98
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.136 SNIP 1.093 CiteScore 3.01
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.944 SNIP 0.957 CiteScore 2.4
ISI indexed (2012): ISI indexed no
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.785 SNIP 0.726 CiteScore 1.94
ISI indexed (2011): ISI indexed no
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.787 SNIP 0.798
Assessment of extracellular matrix-related biomarkers in patients with lower extremity artery disease

The prevalence of lower extremity artery disease (LEAD) is high (20%-25%) in the population older than 65 years, but patients are seldom identified until the disease is advanced. Circulating markers of disease activity might provide patients with a key opportunity for timely treatment. We tested the hypothesis that measuring blood-specific fragments generated during degradation of the extracellular matrix (ECM) could provide further insight into the pathophysiologic mechanism of arterial remodeling. The protein profile of diseased arteries from patients undergoing infragenual limb revascularization was assessed by a liquid chromatography and tandem mass spectrometry, nontargeted proteomic approach. The information retrieved was the basis for measurement of neoepitope fragments of ECM proteins in the blood of 195 consecutive patients with LEAD by specific enzyme-linked immunosorbent assays. Histologic and proteomic analyses confirmed the structural disorganization of affected arteries. Fourteen of 81 proteins were identified as differentially expressed in diseased arteries with respect to healthy tissues. Most of them were related to ECM components, and the difference in expression was used in multivariate analyses to establish that severe arterial lesions in LEAD patients have a specific proteome. Analysis of neoepitope fragments in blood revealed that fragments of versican and collagen type IV, alone or in combination, segregated patients with mild to moderate symptoms (intermittent claudication, Fontaine I-II) from those with severe LEAD (critical limb ischemia, Fontaine III-IV). We propose noninvasive candidate biomarkers with the ability to be clinically useful across the LEAD spectrum.
Biochemical mechanisms determine the functional compatibility of heterologous genes

Elucidating the factors governing the functional compatibility of horizontally transferred genes is important to understand bacterial evolution, including the emergence and spread of antibiotic resistance, and to successfully engineer biological systems. In silico efforts and work using single-gene libraries have suggested that sequence composition is a strong barrier for the successful integration of heterologous genes. Here we sample 200 diverse genes, representing >80% of sequenced antibiotic resistance genes, to interrogate the factors governing genetic compatibility in new hosts. In contrast to previous work, we find that GC content, codon usage, and mRNA-folding energy are of minor importance for the compatibility of mechanistically diverse gene products at moderate expression. Instead, we identify the phylogenetic origin, and the dependence of a resistance mechanism on host physiology, as major factors governing the functionality and fitness of antibiotic resistance genes. These findings emphasize the importance of biochemical mechanism for heterologous gene compatibility, and suggest physiological constraints as a pivotal feature orienting the evolution of antibiotic resistance.
Cameo: A Python Library for Computer Aided Metabolic Engineering and Optimization of Cell Factories

Computational systems biology methods enable rational design of cell factories on a genome-scale and thus accelerate the engineering of cells for the production of valuable chemicals and proteins. Unfortunately, for the majority of these methods’ implementations are either not published, rely on proprietary software, or do not provide documented interfaces, which has precluded their mainstream adoption in the field. In this work we present cameo, a platform-independent software that enables in silico design of cell factories and targets both experienced modelers as well as users new to the field. It is written in Python and implements state-of-the-art methods for enumerating and prioritizing knock-out, knock-in, over-expression, and down-regulation strategies and combinations thereof. Cameo is an open source software project and is freely available under the Apache License 2.0. A dedicated website including documentation, examples, and installation instructions can be found at http://cameo.bio. Users can also give cameo a try at http://try.cameo.bio.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, Global Econometric Modeling, Department of Biotechnology and Biomedicine, iLoop, Department of Chemical and Biochemical Engineering, Synthetic Biology Tools for Yeast, Research Groups
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Journal: A C S Synthetic Biology
ISSN (Print): 2161-5063
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Scopus rating (2017): SNIP 1.107 SJR 2.625
Inflammatory bowel disease (IBD) is a chronic intestinal disorder, with two main types: Crohn’s disease (CD) and ulcerative colitis (UC), whose molecular pathology is not well understood. The majority of IBD-associated SNPs are located in non-coding regions and are hard to characterize since regulatory regions in IBD are not known. Here we profile transcription start sites (TSSs) and enhancers in the descending colon of 94 IBD patients and controls. IBD-upregulated promoters and enhancers are highly enriched for IBD-associated SNPs and are bound by the same transcription factors. IBD-specific TSSs are associated to genes with roles in both inflammatory cascades and gut epithelia while TSSs distinguishing UC and CD are associated to gut epithelia functions. We find that as few as 35 TSSs can distinguish active CD, UC, and controls with 85% accuracy in an independent cohort. Our data constitute a foundation for understanding the molecular pathology, gene regulation, and genetics of IBD.
Chemically controlled interfacial nanoparticle assembly into nanoporous gold films for electrochemical applications

Nanoporous gold (NPG) is an effective material for electrocatalysis and can be made via a dealloy method such as etching of silver–gold alloys. Dealloyed NPG may contain residual silver that affects its catalytic performance. Herein, a different approach has been reported for the formation of NPG at the liquid/air interface starting from gold nanoparticles (AuNPs) in an aqueous solution, providing silver-free gold films. Chloroaucic acid is reduced to AuNP building blocks by 2-(N-morpholino)ethanesulfonic acid, which also acts as a protecting agent and pH buffer. By adding potassium chloride before AuNP synthesis and hydrochloric acid to the resultant AuNP solutions, we can reproducibly obtain continuous gold networks. The sintered AuNPs produced by this method result in chemically synthesized nanoporous gold films (cNPGFs) that resemble dealloyed NPG in terms of morphology and porosity; additionally, they can be controlled by varying the temperature, chloride concentration, ionic strength, and protonation of the buffer. cNPGF formation is attributed to the destabilization of AuNPs at the air–liquid interface. The developed method generates electrochemically stable cNPGFs up to 20 cm² in size with an average thickness of 500 ± 200 nm, areal density of 50–150 μg cm⁻², and porosity as high as 85%. Importantly, cNPGFs can effectively catalyze both CO₂ reduction and CO oxidation electrochemically. Thus, the developed synthetic method offers large-scale production of pure bottom-up NPGFs for multifarious electrocatalytic applications.
Cladosporium species in indoor environments

As part of a worldwide survey of the indoor mycobiota about 520 new Cladosporium isolates from indoor environments mainly collected in China, Europe, New Zealand, North America and South Africa were investigated by using a polyphasic approach to determine their species identity. All Cladosporium species occurring in indoor environments are fully described and illustrated. Forty-six Cladosporium species are treated of which 16 species are introduced as new. A key for the most common Cladosporium species isolated from indoor environments is provided. Cladosporium halotolerans proved to be the most frequently isolated Cladosporium species indoors.

General information

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Organisations: Department of Biotechnology and Biomedicine, Fungal Degradation, Westerdijk Fungal Biodiversity Institute, EMSL Analytical, Inc., University of Pretoria
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 7.224 SJR 6.328
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 14.62 SJR 7.735 SNIP 8.292
Web of Science (2016): Indexed yes
Complete Genome Sequence of *Shewanella* sp. WE21, a Rare Isolate with Multiple Novel Large Genomic Islands

We present here the whole-genome sequence of *Shewanella* sp. WE21, an unusual omega-3 fatty acid-producing bacterium isolated from the gastrointestinal tract of the freshwater fish *Sander vitreus* (walleye). This genome contains a number of unique, large genomic islands with genes not present in other *Shewanella* bacteria.

**General information**

State: Published
Organisations: Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, University of Copenhagen, University of Wisconsin
Authors: Castillo, D. (Ekstern), Gram, L. (Intern), Dailey, F. E. (Ekstern)
Computational prediction of neoantigens: do we need more data or new approaches?

Personalized cancer immunotherapy may benefit from improved computational algorithms for identifying neoantigens. Recent results demonstrate that machine learning can improve accuracy. Additional improvements may require more genomic data paired with in vitro T cell reactivity measurements, and more sophisticated algorithms that take into account T cell receptor specificity.

General information

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Organisations: Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Cancer Genomics
Authors: Eklund, A. C. (Intern), Szallasi, Z. I. (Intern)
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- Scopus rating (2017): SNIP 3.46 SJR 5.599
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): CiteScore 8.09 SJR 5.096 SNIP 3.123
- Web of Science (2016): Indexed yes
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 4.337 SNIP 2.839 CiteScore 7.39
The Brazilian sugarcane industry constitutes one of the biggest and most efficient ethanol production processes in the world. Brazilian ethanol production utilizes a unique process, which includes cell recycling, acid wash, and non-aseptic conditions. Process characteristics, such as extensive CO2 generation, poor quality of raw materials, and frequent contaminations, all lead to excessive foam formation during fermentations, which is treated with antifoam agents (AFA). In this study, we have investigated the impact of industrial AFA treatments on the physiology and transcriptome of the industrial ethanol strain Saccharomyces cerevisiae CAT-1. The investigated AFA included industrially used AFA acquired from Brazilian ethanol plants and commercially available AFA commonly used in the fermentation literature. In batch fermentations, it was shown that industrial AFA compromised growth rates and glucose uptake rates, while commercial AFA had no effect in concentrations relevant for defoaming purposes. Industrial AFA were further tested in laboratory scale simulations of the Brazilian ethanol production process and proved to decrease cell viability compared to the control, and the effects were intensified with increasing AFA concentrations and exposure time. Transcriptome analysis showed that AFA treatments induced additional stress responses in yeast cells compared to the control, shown by an up-regulation of stress-specific genes and a down-regulation of lipid biosynthesis, especially ergosterol. By documenting the detrimental effects associated with chemical AFA, we highlight the importance of developing innocuous systems for foam control in industrial fermentation processes.

Correction to: Industrial antifoam agents impair ethanol fermentation and induce stress responses in yeast cells
The Brazilian sugarcane industry constitutes one of the biggest and most efficient ethanol production processes in the world. Brazilian ethanol production utilizes a unique process, which includes cell recycling, acid wash, and non-aseptic conditions. Process characteristics, such as extensive CO2 generation, poor quality of raw materials, and frequent contaminations, all lead to excessive foam formation during fermentations, which is treated with antifoam agents (AFA). In this study, we have investigated the impact of industrial AFA treatments on the physiology and transcriptome of the industrial ethanol strain Saccharomyces cerevisiae CAT-1. The investigated AFA included industrially used AFA acquired from Brazilian ethanol plants and commercially available AFA commonly used in the fermentation literature. In batch fermentations, it was shown that industrial AFA compromised growth rates and glucose uptake rates, while commercial AFA had no effect in concentrations relevant for defoaming purposes. Industrial AFA were further tested in laboratory scale simulations of the Brazilian ethanol production process and proved to decrease cell viability compared to the control, and the effects were intensified with increasing AFA concentrations and exposure time. Transcriptome analysis showed that AFA treatments induced additional stress responses in yeast cells compared to the control, shown by an up-regulation of stress-specific genes and a down-regulation of lipid biosynthesis, especially ergosterol. By documenting the detrimental effects associated with chemical AFA, we highlight the importance of developing innocuous systems for foam control in industrial fermentation processes.

General information
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Organisations: Department of Biotechnology and Biomedicine, Department of Systems Biology, Regulatory Genomics, Novozymes A/S
Cyclopiamines C and D: Epoxide Spiroindolinone Alkaloids from Penicillium sp. CML 3020

Cyclopiamines C (1) and D (2) were isolated from the extract of Penicillium sp. CML 3020, a fungus sourced from an Atlantic Forest soil sample. Their structures and relative configuration were determined by 1D and 2D NMR, HRMS, and UV/vis data analysis. Cyclopiamines C and D belong to a small subset of rare spiroindolinone compounds containing an alkyl nitro group and a 4,5-dihydro-1H-pyrrolo[3,2,1-ij]quinoline-2,6-dione ring system. NMR and MS/HRMS data confirmed the presence of an epoxide unit (C-17-O-C-18) and a hydroxy group at C-5, not observed for their known congeners. Cytotoxic and antimicrobial activities were evaluated.
Differential bacterial capture and transport preferences facilitate co-growth on dietary xylan in the human gut

Metabolism of dietary glycans is pivotal in shaping the human gut microbiota. However, the mechanisms that promote competition for glycans among gut commensals remain unclear. *Roseburia intestinalis*, an abundant butyrate-producing Firmicute, is a key degrader of the major dietary fibre xylan. Despite the association of this taxon to a healthy microbiota, insight is lacking into its glycan utilization machinery. Here, we investigate the apparatus that confers *R. intestinalis* growth on different xylans. *R. intestinalis* displays a large cell-attached modular xylanase that promotes multivalent and dynamic association to xylan via four xylan-binding modules. This xylanase operates in concert with an ATP-binding cassette transporter to mediate breakdown and selective internalization of xylan fragments. The transport protein of *R. intestinalis* prefers oligomers of 4-5 xylosyl units, whereas the counterpart from a model xylan-degrading *Bacteroides* commensal targets larger ligands. Although *R. intestinalis* and the *Bacteroides* competitor co-grew in a mixed culture on xylan, *R. intestinalis* dominated on the preferred transport substrate xylotetraose. These findings highlight the differentiation of capture and transport preferences as a possible strategy to facilitate co-growth on abundant dietary fibres and may offer a unique route to manipulate the microbiota based on glycan transport preferences in therapeutic interventions to boost distinct taxa.

General information
Dissimilar pigment regulation in Serpula lacrymans and Paxillus involutus during inter-kingdom interactions

Production of basidiomycete atromentin-derived pigments like variegatic acid (pulvinic acid-type) and involutin (diarylcyclopentenone) from the brown-rotter Serpula lacrymans and the ectomycorrhiza-forming Paxillus involutus, respectively, is induced by complex nutrition, and in the case of S. lacrymans, bacteria. Pigmentation in S. lacrymans was stimulated by 13 different bacteria and cell-wall-damaging enzymes (lytic enzymes and proteases), but not by lysozyme or mechanical damage. The use of protease inhibitors with Bacillus subtilis or heat-killed bacteria during co-culturing with S. lacrymans significantly reduced pigmentation indicating that enzymatic hyphal damage and/or released peptides, rather than mechanical injury, was the major cause of systemic pigment induction. Conversely, no significant pigmentation by bacteria was observed from P. involutus. We found additional putative transcriptional composite elements of atromentin synthetase genes in P. involutus and other ectomycorrhiza-forming species that were absent from S. lacrymans and other brown-rotters. Variegatic and its precursor xerocomic acid, but not involutin, in return inhibited swarming and colony biofilm spreading of Bacillus subtilis, but did not kill B. subtilis. We suggest that dissimilar pigment regulation by fungal lifestyle was a consequence of pigment bioactivity and additional promoter motifs. The focus on basidiomycete natural product gene induction and regulation will assist in future studies to determine global regulators, signalling pathways and associated transcription factors of basidiomycetes.
Diversity of Aspergillus section Nigri on the surface of Vitis labrusca and its hybrid grapes

This study investigated the presence of Aspergillus species belonging to Aspergillus section Nigri on Vitis labrusca and its hybrid grapes grown in Brazil. The ability of the fungi isolates to produce ochratoxin A (OTA) and fumonisin B2 (FB2) as well as the presence of these mycotoxins in the grapes were also studied. Eighty-eight samples were collected from the main grape producing states in Brazil: Rio Grande do Sul (n=30), Pernambuco (n=21), São Paulo (n=21) and Paraná (n=16). The highest average contamination level by A. section Nigri occurred on the grapes from Pernambuco (66.3%). A total of 2042 A. section Nigri isolates was analyzed and clustered in three groups according to morphology characterization: A. section Nigri uniseriate (79.3%), A. niger "aggregate" (18.3%) and A. carbonarius (2.4%). In order to precisely identify the Aspergillus species, two hundred and forty-eight strains were subjected to DNA sequencing. Among the A. section Nigri uniseriate group, the following species were found: A. japonicus, A. uvarum, A. brunneoviolaceus, A. aculeatus and A. labruscus. Within the A. niger "aggregate", the following species were found: A. niger sensu stricto, A. welwitschiae and A. vadensis. Regarding mycotoxin-production capacity, 3.2% of the total A. section Nigri isolates (2042) were positive for OTA production and from A. niger "aggregate" (373) tested, 42.1% were FB2 producers. However, none of the 88 grape samples were contaminated with these mycotoxins.

General information
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Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Universidade Estadual de Londrina, Instituto de Tecnologia de Alimentos
Authors: Ferranti, L. D. S. (Ekstern), Fungaro, M. H. P. (Ekstern), Massi, F. P. (Ekstern), Silva, J. J. D. (Ekstern), Penha, R. E. S. (Ekstern), Frisvad, J. C. (Intern), Taniwaki, M. H. (Ekstern), Iamanaka, B. T. (Ekstern)
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Scopus rating (2014): SJR 1.493 SNIP 1.695 CiteScore 3.62
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ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
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ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.607 SNIP 1.713 CiteScore 3.63
ISI indexed (2011): ISI indexed yes
Chronic Pseudomonas aeruginosa infections evade antibiotic therapy and are associated with mortality in cystic fibrosis (CF) patients. We find that in vitro resistance evolution of P. aeruginosa toward clinically relevant antibiotics leads to phenotypic convergence toward distinct states. These states are associated with collateral sensitivity toward several antibiotic classes and encoded by mutations in antibiotic resistance genes, including transcriptional regulator nfxB.

Longitudinal analysis of isolates from CF patients reveals similar and defined phenotypic states, which are associated with extinction of specific sub-lineages in patients. In-depth investigation of chronic P. aeruginosa populations in a CF patient during antibiotic therapy revealed dramatic genotypic and phenotypic convergence. Notably, fluoroquinolone-resistant subpopulations harboring nfxB mutations were eradicated by antibiotic therapy as predicted by our in vitro data. This study supports the hypothesis that antibiotic treatment of chronic infections can be optimized by targeting phenotypic states associated with specific mutations to improve treatment success in chronic infections.

Drug-Driven Phenotypic Convergence Supports Rational Treatment Strategies of Chronic Infections

Chronic Pseudomonas aeruginosa infections evade antibiotic therapy and are associated with mortality in cystic fibrosis (CF) patients. We find that in vitro resistance evolution of P. aeruginosa toward clinically relevant antibiotics leads to phenotypic convergence toward distinct states. These states are associated with collateral sensitivity toward several antibiotic classes and encoded by mutations in antibiotic resistance genes, including transcriptional regulator nfxB.

Longitudinal analysis of isolates from CF patients reveals similar and defined phenotypic states, which are associated with extinction of specific sub-lineages in patients. In-depth investigation of chronic P. aeruginosa populations in a CF patient during antibiotic therapy revealed dramatic genotypic and phenotypic convergence. Notably, fluoroquinolone-resistant subpopulations harboring nfxB mutations were eradicated by antibiotic therapy as predicted by our in vitro data. This study supports the hypothesis that antibiotic treatment of chronic infections can be optimized by targeting phenotypic states associated with specific mutations to improve treatment success in chronic infections.
Effect of alginate size, mannuronic/guluronic acid content and pH on particle size, thermodynamics and composition of complexes with β-lactoglobulin

Alginate is an anionic polysaccharide capable of forming insoluble particles with proteins. Hence, alginate has potential as a protein carrier. However, the role of physical properties of the polysaccharide, such as degree of polymerization (DPn) and mannuronic/guluronic acid ratio, remains to be fully explored. Particle formation of a high and a low molar mass alginate (ALG) with β-lactoglobulin (BLG) at pH 2-8 depends on the average DPn (HMW-ALG: 1.59·10^3; LMW-ALG: 0.23·10^3) and the mannuronic/guluronic acid ratio (1.0; 0.6) as supported by using ManA6 and GulA6 as models. Dynamic light scattering (DLS) showed that particles of BLG with either of the two ALGs have essentially the same hydrodynamic diameter (D_H) at pH 3 and 2, while at pH 4 particles of LMW-ALG/BLG have larger D_H than of HMW-ALG/BLG. At pH 5-8 no significant particle formation was observed. ManA6 did not form insoluble particles at pH 2-8, while GulA6 formed insoluble particles, albeit only at pH 4. K_d was approximately 10-fold higher for LMW-ALG/BLG than HMW-ALG/BLG and 3 orders of magnitude higher for an alginate trisaccharide/BLG complexation as determined by isothermal titration calorimetry (ITC). The alginate trisaccharide did not form insoluble particles with BLG at pH 3 and 4, though interaction still occurred. δH_app and molar stoichiometry of BLG in the complexes with the two ALGs differed by a factor of 7, as did their DPn, which thus affected the interaction strength, but not the BLG content. At pH 4 the BLG content doubled in the particle due to BLG dimerization. The findings emphasize the importance of DPn, mannuronic/guluronic acid ratio and pH in formulations containing alginate/whey protein particles.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Protein Glycoscience and Biotechnology, Department of Micro- and Nanotechnology, Amphiphilic Polymers in Biological Sensing, University of Copenhagen, DuPont, Roskilde University
Authors: Stender, E. G. (Intern), Khan, S. (Intern), Ipsen, R. (Ekstern), Madsen, F. (Ekstern), Hägglund, P. (Intern), Hachem, M. A. (Intern), Almdal, K. (Intern), Westh, P. (Ekstern), Svensson, B. (Intern)
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.1 SJR 2.03 SNIP 2.045
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.802 SNIP 1.924 CiteScore 4.53
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 2.232 SNIP 2.554 CiteScore 5.21
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 2.098 SNIP 2.256 CiteScore 4.81
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.837 SNIP 2.06 CiteScore 3.69
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 1.618 SNIP 1.911 CiteScore 3.57
The present work was targeted to design a surface against cell seeding and adhering of bacteria, Bacillus subtilis. A multi-walled carbon nanotube/titanium dioxide nano-power was produced via simple mixing of carbon nanotube and titanium dioxide nanoparticles during the sol-gel process followed by heat treatment. Successfully, quercetin was immobilized on the nanocomposite via physical adsorption to form a quercetin/multi-walled carbon nanotube/titanium dioxide nanocomposite. The adhesion of bacteria on the coated-slides was verified after 24 h using confocal laser-scanning microscopy. Results indicated that the quercetin/multi-walled carbon nanotube/titanium dioxide nanocomposite had more negativity and higher recovery by glass surfaces than its counterpart. Moreover, coating surfaces with the quercetin-modified nanocomposite lowered both hydrophilicity and surface-attached bacteria compared to surfaces coated with the multi-walled carbon nanotubes/titanium dioxide nanocomposite.
Effect of TDA-producing *Phaeobacter inhibens* on the fish pathogen *Vibrio anguillarum* in non-axenic algae and copepod systems

The expanding aquaculture industry plays an important role in feeding the growing human population and with the expansion, sustainable bacterial disease control, such as probiotics, becomes increasingly important. Tropodithietic acid (TDA)-producing *Phaeobacter* spp. can protect live feed, for example rotifers and *Artemia* as well as larvae of turbot and cod against pathogenic vibrios. Here, we show that the emerging live feed, copepods, is unaffected by colonization of the fish pathogen *Vibrio anguillarum*, making them potential infection vectors. However, TDA-producing *Phaeobacter inhibens* was able to significantly inhibit *V. anguillarum* in non-axenic cultures of copepod *Acartia tonsa* and the copepod feed *Rhodomonas salina*. *Vibrio* grew to $10^6$ CFU ml$^{-1}$ and $10^7$ CFU ml$^{-1}$ in copepod and *R. salina* cultures, respectively. However, vibrio counts remained at the inoculum level (10$^4$ CFU ml$^{-1}$) when *P. inhibens* was also added. We further developed a semi-strain-specific qPCR for *V. anguillarum* to detect and quantify the pathogen in non-axenic systems. In conclusion, *P. inhibens* efficiently inhibits the fish larval pathogen *V. anguillarum* in the emerging live feed, copepods, supporting its use as a probiotic in aquaculture. Furthermore, qPCR provides an effective method for detecting vibrio pathogens in complex non-axenic live feed systems.
Efficient Oligo nucleotide mediated CRISPR-Cas9 Gene Editing in Aspergilli

CRISPR-Cas9 technologies are revolutionizing fungal gene editing. Here we show that survival of specific Cas9/sgRNA mediated DNA double strand breaks (DSBs) depends on the non-homologous end-joining, NHEJ, DNA repair pathway and we use this observation to develop a tool to assess protospacer efficiency in Aspergillus nidulans. Moreover, we show that in NHEJ deficient strains, highly efficient marker-free gene targeting can be performed. Indeed, we show that even single-stranded oligo nucleotides efficiently works as repair templates of specific Cas9/sgRNA induced DNA DSBs in A. nidulans, A. niger, and in A. oryzae indicating that this type of repair may be wide spread in filamentous fungi. Importantly, we demonstrate that by using single-stranded oligo nucleotides for CRISPR-Cas9 mediated gene editing it is possible to introduce specific point mutations as well gene deletions at efficiencies approaching 100%. The efficiency of the system invites for multiplexing and we have designed a vector system with the capacity of delivering Cas9 and multiple sgRNAs based on polymerase III promoters and tRNA spacers. We show that it is possible to introduce two point mutations and one gene insertion in one transformation experiment with a very high efficiency. Our system is compatible with future high-throughput gene-editing experiments.

General information
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Publication information
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Volume: 115
ISSN (Print): 1087-1845
Ratings:
Evaluation of synthetic promoters in *Physcomitrella patens*

Securing a molecular toolbox including diverse promoters is essential for genome engineering. However, native promoters have limitations such as the available number or the length of the promoter. In this work, three short synthetic promoters
were characterized by using the yellow fluorescent protein Venus. All of the tested promoters were active and showed higher mRNA expression than housekeeping gene *PpAct7*, and similar protein expression level to the *AtUBQ10* promoter. This study shows that few cis-regulatory elements are enough to establish a strong promoter for continuous expression of genes in plants. Along with this, the study enhances the number of available promoters to be used in *P. patens*. It also demonstrates the potential to construct multiple non-native promoters on demand, which would aid to resolve one bottleneck in multiple pathway expression in *P. patens* and other plants.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, Photosynthetic Cell Factories, Synpromics
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Scopus rating (2017): SNIP 0.707 SJR 1.087
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.51 SJR 1.133 SNIP 0.699
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.18 SNIP 0.704 CiteScore 2.43
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.179 SNIP 0.718 CiteScore 2.37
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.282 SNIP 0.757 CiteScore 2.62
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.282 SNIP 0.763 CiteScore 2.65
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.343 SNIP 0.777 CiteScore 2.65
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.397 SNIP 0.769
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.436 SNIP 0.767
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.519 SNIP 0.809
Scopus rating (2007): SJR 1.564 SNIP 0.814
Scopus rating (2006): SJR 1.591 SNIP 0.817
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.58 SNIP 0.819
Scopus rating (2004): SJR 1.566 SNIP 0.8
Scopus rating (2003): SJR 1.525 SNIP 0.796
Scopus rating (2002): SJR 1.57 SNIP 0.808
Evidence of No Association Between Human Papillomavirus and Breast Cancer

Background: Globally, breast cancer is the most frequent cancer among women. Studies reported an increased risk of breast cancer among women with prior cervical dysplasia. This study aimed to describe the prevalence of human papillomavirus (HPV) in breast cancer and explore if women with prior cervical neoplasia carry an increased risk of HPV-positive breast cancer compared to women without.

Methods: This case–control study identified 193 Danish women diagnosed with breast cancer (1998–2012) at Aarhus University Hospital or Copenhagen University Hospital Herlev. Cases were 93 women with cervical intraepithelial neoplasia grade 3 or worse (CIN3+) prior to breast cancer. Controls were 100 women without prior cervical dysplasia. HPV testing and genotyping were done using SPF10 PCR-DEIA-LIPA25 and an in-house semi-Q-PCR assay.

Results: Overall HPV prevalence in breast cancer for the assays was 1.55% (95% CI 0.32–4.48) and 0.52% (95% CI 0.01–2.85). There was no difference in HPV prevalence between cases and controls (2.15 vs. 1.00%, p = 0.61 and 1.08 vs. 0.00%, p = 0.48). HPV prevalence in CIN3+ was 94.62% (95% CI 0.88–0.98). Concordance between the assays was 98.60%.

Conclusion: HPV prevalence in breast cancer is very low suggesting no etiological correlation between HPV and breast cancer.

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Organisations: Department of Biotechnology and Biomedicine, National Veterinary Institute, Bacterial Ecophysiology and Biotechnology, Bacteriology & Parasitology, Odense University Hospital, University Hospital Herlev, Aarhus University, Copenhagen University Hospital, Private Gynecological Clinic Suzan Lenz Gynaekolog, Aarhus University Hospital
Authors: Bønløkke, S. (Forskerdatabase), Blaakær, J. (Forskerdatabase), Steiniche, T. (Ekstern), Høgdall, E. (Ekstern), Jensen, S. G. (Forskerdatabase), Hammer, A. (Forskerdatabase), Balslev, E. (Forskerdatabase), Strube, M. L. (Intern), Knakkergaard, H. (Ekstern), Lenz, S. (Ekstern)
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Evolution of exploitative interactions during diversification in Bacillus subtilis biofilms
Microbial biofilms are tightly packed, heterogeneous structures that serve as arenas for social interactions. Studies on Gram negative models reveal that during evolution in structured environments like biofilms, isogenic populations
commonly diversify into phenotypically and genetically distinct variants. These variants can settle in alternative biofilm niches and develop new types of interactions that greatly influence population productivity. Here, we explore the evolutionary diversification of pellicle biofilms of the Gram positive, spore-forming bacterium Bacillus subtilis. We discover that-similarly to other species-B. subtilis diversifies into distinct colony variants. These variants dramatically differ in biofilm formation abilities and expression of biofilm-related genes. In addition, using a quantitative approach, we reveal striking differences in surface complexity and hydrophobicity of the evolved colony types. Interestingly, one of the morphotypes completely lost the ability of independent biofilm formation and evolved to hitchhike with other morphotypes with improved biofilm forming abilities. Genome comparison suggests that major phenotypic transformations between the morphotypes can be triggered by subtle genetic differences. Our work demonstrates how positive complementarity effects and exploitative interactions intertwine during evolutionary diversification in biofilms.

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Organisations: Department of Biotechnology and Biomedicine, Friedrich-Schiller-Universitat Jena, Seqomics Biotechnology Ltd, Hungarian Academy of Sciences, Technical University of Munich, Technical University of Denmark
Authors: Dragoš, A. (Ekstern), Lakshmanan, N. (Ekstern), Martin, M. (Ekstern), Horváth, B. (Ekstern), Maróti, G. (Ekstern), García, C. F. (Ekstern), Lieleg, O. (Ekstern), Kovács, Á. T. (Intern)
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 3.85
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 3.77
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 3.8
Web of Science (2014): Indexed yes
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ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 3.78
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 3.63
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Web of Science (2008): Indexed yes
Exploring the Effect of Phage Therapy in Preventing *Vibrio anguillarum* Infections in Cod and Turbot Larvae

The aquaculture industry is suffering from losses associated with bacterial infections by opportunistic pathogens. *Vibrio anguillarum* is one of the most important pathogens, causing vibriosis in fish and shellfish cultures leading to high mortalities and economic losses. Bacterial resistance to antibiotics and inefficient vaccination at the larval stage of fish emphasizes the need for novel approaches, and phage therapy for controlling *Vibrio* pathogens has gained interest in the past few years. In this study, we examined the potential of the broad-host-range phage KVP40 to control four different *V. anguillarum* strains in Atlantic cod (*Gadus morhua* L.) and turbot (*Scophthalmus maximus* L.) larvae. We examined larval mortality and abundance of bacteria and phages. Phage KVP40 was able to reduce and/or delay the mortality of the cod and turbot larvae challenged with *V. anguillarum*. However, growth of other pathogenic bacteria naturally occurring on the fish eggs prior to our experiment caused mortality of the larvae in the unchallenged control groups. Interestingly, the broad-spectrum phage KVP40 was able to reduce mortality in these groups, compared to the nonchallenge control groups not treated with phage KVP40, demonstrating that the phage could also reduce mortality imposed by the background population of pathogens. Overall, phage-mediated reduction in mortality of cod and turbot larvae in experimental challenge assays with *V. anguillarum* pathogens suggested that application of broad-host-range phages can reduce *Vibrio*-induced mortality in turbot and cod larvae, emphasizing that phage therapy is a promising alternative to traditional treatment of vibriosis in marine aquaculture.

General information

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Organisations: Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, University of Copenhagen, University of Bergen, Hellenic Centre for Marine Research, Fishlab, ACD Pharmaceuticals AS
Authors: Rørbo, N. (Ekstern), Rønneseth, A. (Ekstern), Kalatzis, P. G. (Ekstern), Rasmussen, B. B. (Intern), Engell-Sørensen, K. (Ekstern), Kleppen, H. P. (Ekstern), Wergeland, H. I. (Ekstern), Gram, L. (Intern), Middelboe, M. (Ekstern)
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- Scopus rating (2016): SNIP 0.676 SJR 0.714
- Scopus rating (2015): SNIP 0.552 SJR 0.44
- Scopus rating (2014): SNIP 0.608 SJR 0.365
- Scopus rating (2013): SNIP 0.093 SJR 0.176
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DOIs:
Exposure of tropoelastin to peroxynitrous acid gives high yields of nitrated tyrosine residues, di-tyrosine cross-links and altered protein structure and function

Elastin is an abundant extracellular matrix protein in elastic tissues, including the lungs, skin and arteries, and comprises 30–57% of the aorta by dry mass. The monomeric precursor, tropoelastin (TE), undergoes complex processing during elastogenesis to form mature elastic fibres. Peroxynitrous acid (ONOOH), a potent oxidising and nitrating agent, is formed in vivo from superoxide and nitric oxide radicals. Considerable evidence supports ONOOH formation in the inflamed artery wall, and a role for this species in the development of human atherosclerotic lesions, with ONOOH-damaged extracellular matrix implicated in lesion rupture. We demonstrate that TE is highly sensitive to ONOOH, with this resulting in extensive dimerization, fragmentation and nitration of Tyr residues to give 3-nitrotyrosine (3-nitroTyr). This occurs with equimolar or greater levels of oxidant and increases in a dose-dependent manner. Quantification of Tyr loss and 3-nitroTyr formation indicates extensive Tyr modification with up to two modified Tyr per protein molecule, and up to 8% conversion of initial ONOOH to 3-nitroTyr. These effects were modulated by bicarbonate, an alternative target for ONOOH. Inter- and intra-protein di-tyrosine cross-links have been characterized by mass spectrometry. Examination of human atherosclerotic lesions shows colocalization of 3-nitroTyr with elastin epitopes, consistent with TE or elastin modification in vivo, and also an association of 3-nitroTyr containing proteins and elastin with lipid deposits. These data suggest that exposure of TE to ONOOH gives marked chemical and structural changes to TE and altered matrix assembly, and that such damage accumulates in human arterial tissue during the development of atherosclerosis.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Center for Biological Sequence Analysis, Proteomics Platform, DTU Proteomics Core, The Heart Research Institute, University of Copenhagen, Medical University of Graz
Authors: Degendorfer, G. (Ekstern), Chuang, C. Y. (Forskerdatabase), Mariotti, M. (Intern), Hammer, A. (Ekstern), Hoefler, G. (Ekstern), Hägglund, P. (Intern), Malle, E. (Ekstern), Wise, S. G. (Ekstern), Davies, M. J. (Ekstern)
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.518 SNIP 1.623 CiteScore 5.89
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.469 SNIP 1.653 CiteScore 5.86
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.239 SNIP 1.69 CiteScore 5.81
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.116 SNIP 1.66 CiteScore 5.51
Familial co-occurrence of congenital heart defects follows distinct patterns

Congenital heart defects (CHD) affect almost 1% of all live born children and the number of adults with CHD is increasing. In families where CHD has occurred previously, estimates of recurrence risk, and the type of recurring malformation are important for counselling and clinical decision-making, but the recurrence patterns in families are poorly understood. We aimed to determine recurrence patterns, by investigating the co-occurrences of CHD in 1163 families with known malformations, comprising 3080 individuals with clinically confirmed diagnosis. We calculated rates of concordance and discordance for 41 specific types of malformations, observing a high variability in the rates of concordance and discordance. By calculating odds ratios for each of 1640 pairs of discordant lesions observed between affected family members, we were able to identify 178 pairs of malformations that co-occurred significantly more or less often than expected in families. The data show that distinct groups of cardiac malformations co-occur in families, suggesting influence from underlying developmental mechanisms. Analysis of human and mouse susceptibility genes showed that they were shared in 19% and 20% of pairs of co-occurring discordant malformations, respectively, but none of malformations that rarely co-occur, suggesting that a significant proportion of co-occurring lesions in families is caused by overlapping susceptibility genes. Familial CHD follow specific patterns of recurrence, suggesting a strong influence from genetically regulated developmental mechanisms. Co-occurrence of malformations in families is caused by shared susceptibility genes.

General information

State: Published
Organisations: Department of Biotechnology and Biomedicine, Regulatory Genomics, University of Copenhagen, Hospices Civils de Lyon, Georgetown University Medical Center, The Ohio State University, Cincinnati Children's Hospital Medical Center, Academic Medical Center, Newcastle University, Aarhus University Hospital
Pages: 1015-1022
Publication date: 2018
Main Research Area: Technical/natural sciences
Kirromycin is the main product of the soil-dwelling Streptomyces collinus Tü 365. The elucidation of the biosynthetic pathway revealed that the antibiotic is synthesised via a unique combination of trans-/cis-AT type I polyketide synthases and non-ribosomal peptide synthetases (PKS I/NRPS). This was the first example of an assembly line integrating the three biosynthetic principles in one pathway. However, information about other enzymes involved in kirromycin biosynthesis remained scarce. In this study, genes encoding tailoring enzymes KirM, KirHVI, KirOI, and KirOII, and the putative crotonyl-CoA reductase/carboxylase KirN were deleted, complemented, and the emerged products analysed by HPLC-HRMS and MS/MS. Derivatives were identified in mutants ΔkirM, ΔkirHVI, ΔkirOI, and ΔkirOII. The products of ΔkirOI, ΔkirOII, and kirHVI were subjected to 2D-NMR for structure elucidation. Our results enabled functional assignment of those enzymes, demonstrating their involvement in kirromycin tailoring. In the ΔkirN mutant, the production of kirromycin was significantly decreased. The obtained data enabled us to clarify the putative roles of the studied enzymes, ultimately allowing us to fill many of the missing gaps in the biosynthesis of the complex antibiotic. Furthermore, this collection of mutants can serve as a toolbox for generation of new kirromycins.
Genetic manipulation of structural color in bacterial colonies

Naturally occurring photonic structures are responsible for the bright and vivid coloration in a large variety of living organisms. Despite efforts to understand their biological functions, development, and complex optical response, little is known of the underlying genes involved in the development of these nanostructures in any domain of life. Here, we used Flavobacterium colonies as a model system to demonstrate that genes responsible for gliding motility, cell shape, the stringent response, and tRNA modification contribute to the optical appearance of the colony. By structural and optical analysis, we obtained a detailed correlation of how genetic modifications alter structural color in bacterial colonies. Understanding of genotype and phenotype relations in this system opens the way to genetic engineering of on-demand living optical materials, for use as paints and living sensors.
Glycoengineering in CHO cells: Advances in systems biology

For several decades, glycoprotein biologics have been successfully produced from Chinese hamster ovary (CHO) cells. The therapeutic efficacy and potency of glycoprotein biologics are often dictated by their post translational modifications, particularly glycosylation, which unlike protein synthesis, is a non-templated process. Consequently, both native and recombinant glycoprotein production generate heterogeneous mixtures containing variable amounts of different glycoforms. Stability, potency, plasma half-life, and immunogenicity of the glycoprotein biologic are directly influenced by the glycoforms. Recently, CHO cells have also been explored for production of therapeutic glycosaminoglycans (e.g. heparin), which presents similar challenges as producing glycoproteins biologics. Approaches to controlling heterogeneity in CHO cells and directing the biosynthetic process toward desired glycoforms are not well understood. A systems biology approach combining different technologies is needed for complete understanding of the molecular processes accounting for this variability and to open up new venues in cell line development. In this review, we describe several advances in genetic manipulation, modeling, and glycan and glycoprotein analysis that together will provide new strategies for glycoengineering of CHO cells with desired or enhanced glycosylation capabilities.

General information

State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, SUNY Polytechnic Institute, Export-Import Bank of Korea
High-fat feeding induces mobilization of vitamin C in obese prone rats

In obesity and dyslipidemia, hydrolysis of triacylglycerol (TAG) into non-esterified fatty acids (NEFAs) may contribute to insulin resistance, and production of oxygenated, bioactive polyunsaturated fatty acids may increase oxidative stress. Here we show that after six weeks of high-fat feeding of obese prone rats (Crl:OP(CD), vitamin C was increased both in liver (P<0.01) and plasma (P<0.001), while both TAG (P<0.01) and NEFA (P<0.001) were lower than in low-fat fed control rats. Hepatic vitamin C biosynthesis was similar between groups, indicating that a new steady state level was established with a higher vitamin C level adequate for supplying the systemic needs. Glucose and insulin sensitivity were unaffected at
this stage. Eventually, the mobilization of vitamin C may be seen as a mechanism to protect the host against insulin resistance.

General information
State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, University of Copenhagen
Authors: Tranberg, B. (Ekstern), Hellgren, L. (Intern), Lykkesfeldt, J. (Ekstern), Hansen, A. (Ekstern)
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Journal: Research in Veterinary Science
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BFI (2017): BFI-level 2
Scopus rating (2017): SJR 0.593 SNIP 0.941
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): SJR 0.646 SNIP 0.779 CiteScore 1.46
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 0.774 SNIP 0.933 CiteScore 1.57
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 0.687 SNIP 0.887 CiteScore 1.58
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 0.691 SNIP 0.945 CiteScore 1.62
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 0.633 SNIP 1.067 CiteScore 1.63
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 0.726 SNIP 1.054 CiteScore 1.65
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 0.631 SNIP 0.98
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 0.609 SNIP 1.009
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.569 SNIP 0.941
Scopus rating (2007): SJR 0.558 SNIP 1.048
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.591 SNIP 1.191
Scopus rating (2005): SJR 0.647 SNIP 0.924
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.577 SNIP 0.954
Scopus rating (2003): SJR 0.543 SNIP 0.74
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.514 SNIP 1.045
Scopus rating (2001): SJR 0.503 SNIP 0.988
High-Throughput In Vitro Screening for Inhibitors of Cereal α-Glucosidase

The hydrolysis of starch is a key step in plant germination, which also has relevance in the malting and brewing processes for beer and spirit production. Gaps in knowledge about this metabolic process exist that cannot easily be addressed using traditional genetic techniques, due to functional redundancy in many of the enzyme activities required for alpha-glucan metabolism in cereal crop species. Chemical inhibitors provide opportunities to probe the role of carbohydrate-active enzymes and the phenotypes associated with inhibition of specific enzymes. Iminosugars are the largest group of carbohydrate-active enzyme inhibitors and represent an underused resource for the dissection of plant carbohydrate metabolism. Herein we report a method for carrying out a reverse chemical genetic screen on α-glucosidase, the enzyme that catalyzes the final step in starch degradation during plant germination, namely the hydrolysis of maltose to release glucose. This chapter outlines the use of a high-throughput screen of small molecules for inhibition of α-glucosidase using a colorimetric assay which involves the substrate p-nitrophenyl α-D-glucopyranoside. Identified inhibitors can be further utilized in phenotypic screens to probe the roles played by amylolytic enzymes. Furthermore this 96-well plate-based method can be adapted to assay exo-glycosidase activities involved in other aspects of carbohydrate metabolism.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, John Innes Centre
Authors: Rugen, M. D. (Ekstern), Rejzek, M. (Ekstern), Næsted, H. (Intern), Svensson, B. (Intern), Field, R. A. (Ekstern)
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IFN-λ and microRNAs are important modulators of the pulmonary innate immune response against influenza A (H1N2) infection in pigs
The innate immune system is paramount in the response to and clearance of influenza A virus (IAV) infection in non-immune individuals. Known factors include type I and III interferons and antiviral pathogen recognition receptors, and the cascades of antiviral and pro- and anti-inflammatory gene expression they induce. MicroRNAs (miRNAs) are increasingly recognized to participate in post-transcriptional modulation of these responses, but the temporal dynamics of how these players of the antiviral innate immune response collaborate to combat infection remain poorly characterized. We quantified the expression of miRNAs and protein coding genes in the lungs of pigs 1, 3, and 14 days after challenge with swine IAV (H1N2). Through RT-qPCR we observed a 400-fold relative increase in IFN-lambda 3 gene expression on day 1 after challenge, and a strong interferon-mediated antiviral response was observed on days 1 and 3 accompanied by up-regulation of genes related to the pro-inflammatory response and apoptosis. Using small RNA sequencing and qPCR validation we found 27 miRNAs that were differentially expressed after challenge, with the highest number of regulated miRNAs observed on day 3. In contrast, the number of protein coding genes found to be regulated due to IAV infection
peaked on day 1. Pulmonary miRNAs may thus be aimed at fine-tuning the initial rapid inflammatory response after IAV infection. Specifically, we found five miRNAs (ssc-miR-15a, ssc-miR-18a, ssc-miR-21, ssc-miR-29b, and hsa-miR-590-3p)-four known porcine miRNAs and one novel porcine miRNA candidate-to be potential modulators of viral pathogen recognition and apoptosis. A total of 11 miRNAs remained differentially expressed 14 days after challenge, at which point the infection had cleared. In conclusion, the results suggested a role for miRNAs both during acute infection as well as later, with the potential to influence lung homeostasis and susceptibility to secondary infections in the lungs of pigs after IAV infection.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, National Veterinary Institute, Innate Immunology, Virology, University of Copenhagen, Robert Koch Institute
Authors: Brogaard, L. (Intern), Larsen, L. E. (Intern), Heegaard, P. M. H. (Intern), Anthon, C. (Ekstern), Gorodkin, J. (Ekstern), Duerrwald, R. (Ekstern), Skovgaard, K. (Intern), Renukaradhya, G. J. (ed.) (Ekstern)
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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.425 SNIP 1.233 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.705 SNIP 1.178
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.614 SNIP 1.046
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Impact of CHO Metabolism on Cell Growth and Protein Production: An Overview of Toxic and Inhibiting Metabolites and Nutrients

For over three decades, Chinese hamster ovary (CHO) cells have been the chosen expression platform for the production of therapeutic proteins with complex post-translational modifications. However, the metabolism of these cells is far from perfect and optimized, and requires substantial knowhow and process optimization and monitoring to perform efficiently. One of the main reasons for this is the production and accumulation of toxic and growth-inhibiting metabolites during culture. Lactate and ammonium are the most known, but many more have been identified. In this review, we present an overview of metabolites that deplete and accumulate throughout the course of cultivations with toxic and growth inhibitory effects to the cells. We further provide an overview of the CHO metabolism with emphasis to metabolic pathways of amino acids, glutathione (GSH), and related compounds which have growth-inhibiting and/or toxic effect on the cells. Additionally, we survey relevant publications which describe the applications of metabolomics as a powerful tool for revealing which reactions occur in the cell under certain conditions and identify growth-inhibiting and toxic metabolite. We also present a number of resources that describe the cellular mechanisms of CHO and are available on-line. Finally, we discuss the application of this knowledge for bioprocess and medium development and cell line engineering.

General information
State: Accepted/In press
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Pereira, S. (Intern), Kildegaard, H. F. (Intern), Andersen, M. R. (Intern)
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Impaired competence in flagellar mutants of Bacillus subtilis is connected to the regulatory network governed by DegU:
Running title: Hindered competence by lack of motility
The competent state is a developmentally distinct phase, in which bacteria are able to take up and integrate exogenous DNA into their genome. Bacillus subtilis is one of the naturally competent bacterial species and the domesticated laboratory strain 168 is easily transformable. In this study, we report a reduced transformation frequency of B. subtilis mutants lacking functional and structural flagellar components. This includes hag, the gene encoding the flagellin protein
forming the filament of the flagellum. We confirm that the observed decrease of the transformation frequency is due to reduced expression of competence genes, particularly of the main competence regulator comK. The impaired competence is due to an increase in the phosphorylated form of the response regulator DegU, which is involved in regulation of both flagellar motility and competence. Altogether, our study identified a close link between motility and natural competence in B. subtilis suggesting that hindrance in motility has great impact on differentiation of this bacterium not restricted only to the transition towards sessile growth stage.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, Max Planck Institut fur Chemische Okologie, Friedrich-Schiller-Universität Jena
Authors: Hölscher, T. (Ekstern), Schiklang, T. (Ekstern), Dragos, A. (Ekstern), Dietel, A. (Ekstern), Kost, C. (Ekstern), Kovács, Á. T. (Intern)
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- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): CiteScore 3.47 SJR 1.504 SNIP 0.935
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- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 1.646 SNIP 0.979 CiteScore 3.39
- Web of Science (2015): Indexed yes
- BFI (2014): BFI-level 1
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- Web of Science (2014): Indexed yes
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 1.496 SNIP 0.944 CiteScore 3.24
- ISI indexed (2013): ISI indexed yes
- Scopus rating (2012): SJR 1.48 SNIP 0.913 CiteScore 2.99
- ISI indexed (2012): ISI indexed yes
- Web of Science (2012): Indexed yes
- Scopus rating (2011): SJR 1.664 SNIP 1.237 CiteScore 2.77
- ISI indexed (2011): ISI indexed no
- Scopus rating (2010): SJR 1.287 SNIP 0.928

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Publication: Research - peer-review › Journal article – Annual report year: 2018
Interaction between structurally different heteroexopolysaccharides and β-lactoglobulin studied by solution scattering and analytical ultracentrifugation

Despite a very large number of bacterial exopolysaccharides have been reported, detailed knowledge on their molecular structures and associative interactions with proteins is lacking. Small-angle X-ray scattering, dynamic light scattering and analytical ultracentrifugation (AUC) were used to characterize the interactions of six lactic acid bacterial heteroexopolysaccharides (HePS-1-HePS-6) with β-lactoglobulin (BLG). Compared to free HePSs, a large increase in the X-ray radius of gyration RG, maximum length L and hydrodynamic diameter dH of HePS-1-HePS-4 mixed with BLG revealed strong aggregation, the extent of which depended on the compact conformation and degree of branching of these HePSs. No significant effects were observed with HePS-5 and HePS-6. Turbidity and AUC analyses showed that both soluble and insoluble BLG-HePS complexes were formed. The findings provide new insights into the role of molecular structures in associative interactions between HePSs and BLG which has relevance for various industrial applications.

General information
State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Department of Micro- and Nanotechnology, Enzyme and Protein Chemistry, Department of Chemistry, X-ray Crystallography, Amphiphilic Polymers in Biological Sensing, Agriculture and Agri-Food Canada, University of Copenhagen
Authors: Khan, S. (Intern), Birch, J. (Intern), Van Calsteren, M. (Ekstern), Ipsen, R. (Ekstern), Peters, G. H. (Intern), Svensson, B. (Intern), Harris, P. (Intern), Almdal, K. (Intern)
Publication date: 2018
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BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.307 SJR 0.917
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.84 SJR 0.882 SNIP 1.294
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.808 SNIP 1.303 CiteScore 3.38
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.864 SNIP 1.32 CiteScore 3.13
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.848 SNIP 1.431 CiteScore 3.48
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.787 SNIP 1.302 CiteScore 2.77
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.692 SNIP 1.198 CiteScore 2.73
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.873 SNIP 1.201
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.806 SNIP 1.183
Pyrimidine nucleotides play an important role in the biosynthesis of activated nucleotide sugars (NDP-sugars). NDP-sugars are the precursors of structural polysaccharides in bacteria, including capsule, which is a major virulence factor of the human pathogen S. pneumoniae. In this work, we identified a spontaneous non-reversible mutant of strain D39 that displayed a non-producing capsule phenotype. Whole-genome sequencing analysis of this mutant revealed several non-synonymous single base modifications, including in genes of the de novo synthesis of pyrimidines and in the -10 box of capsule operon promoter (Pops). By directed mutagenesis we showed that the point mutation in Pcps was solely responsible for the drastic decrease in capsule expression. We also demonstrated that D39 subjected to uracil deprivation shows increased biomass and decreased Pcps activity and capsule amounts. Importantly, Pcps expression is further decreased by mutating the first gene of the de novo synthesis of pyrimidines, carA. In contrast, the absence of uracil from the culture medium showed no effect on the spontaneous mutant strain. Co-cultivation of the wild-type and the mutant strain indicated a competitive advantage of the spontaneous mutant (non-producing capsule) in medium devoid of uracil. We propose a model in that uracil may act as a signal for the production of different capsule amounts in S. pneumoniae.
Isoenergetic modification of whey protein structure by denaturation and crosslinking using transglutaminase

Transglutaminase (TG) catalyzes formation of covalent bonds between lysine and glutamine side chains and has applications in manipulation of food structure. Physical properties of a whey protein mixture (SPC) denatured either at elevated pH or by heat-treatment and followed by TG catalyzed crosslinking, have been characterised using dynamic light scattering, size exclusion chromatography, fluorescence spectroscopy and atomic force microscopy. The degree of enzymatic crosslinking appeared higher for pH- than for heat-denatured SPC. The hydrophobic surface properties depended on the treatment, thus heating caused the largest exposure of the hydrophobic core of SPC proteins, which was decreased by crosslinking. The particle size of the treated SPC samples increased upon crosslinking by TG. Moreover, the particle morphology depended on the type of denaturing treatment, thus heat-treated SPC contained fibrillar structures, while pH-denatured SPC remained globular as documented by using atomic force microscopy. Finally, the in vitro digestability of the different SPC samples was assessed under simulated gastric and intestinal conditions. Notably heat-treatment was found to lower the gastric digestion rate and enzymatic crosslinking reduced both the gastric and the intestinal rate of digestion. These characteristics of the various SPC samples provide a useful basis for design of isoenergetic model foods applicable in animal and human studies on how food structure affects satiety.

General information
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Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Department of Micro- and Nanotechnology, Amphiphilic Polymers in Biological Sensing, University of Leeds, University of Copenhagen
Authors: Stender, E. G. P. (Intern), Koutina, G. (Ekstern), Almdal, K. (Intern), Hassenkam, T. (Ekstern), Mackie, A. (Ekstern), Ipsen, R. (Ekstern), Svensson, B. (Intern)
Number of pages: 9
Publication date: 2018
Main Research Area: Technical/natural sciences

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Isolation and characterization of bacteriophages with therapeutic potential

The concerning spread of antibiotic resistant bacteria has directed the spotlight upon bacteriophages, in short phages, as potential candidates for therapeutic purposes. Far from being a novelty, phage therapy has been widely used in the 20s and 30s in western countries until the discovery of antibiotics, which, coupled with a lack of knowledge of phage biology at that time, led to the replacement of phage therapy by antibiotics. On the other side of the planet, the Georgian Eliava Institute has been using phages for treating bacterial diseases since short after phage discovery a century ago. Georgian pharmacies commonly sell phage cocktails from the Institute without the need of a doctor's prescription. A thorough characterisation of the cocktail is though required for it to be accepted as pharmaceutical in the European Union. The potential to investigate the genetic material of microbial communities directly from the environment through metagenomics, allows for genomic characterisation of these cocktail. Furthermore, metagenomics analyses may lead to the discovery of novel phages with therapeutic potential, opening up a promising new horizon for phage therapy.

This thesis is divided into five parts, each assigned a chapter. Chapter 1 provides the reader with an introduction to phage biology, history and metagenomics. Here, the main bioinformatics methods used throughout the studies of the following chapters are also presented and briefly described. Chapter 2 presents the paper "HostPhinder: A Phage Host Prediction Tool" published in May 2016. The tool predicts the bacterial host of a given phage based on co-occurrent k-mers between a query sequence and reference phage genomes with known host. HostPhinder's accuracy in predicting the host species and genus of an evaluation set was higher than 74% and 81%, respectively. The tool can be applied to identify the host of phage sequences found for instance in metagenomes allowing for a first step characterisation. Chapter 3 presents the paper "Metagenomic analysis of therapeutic PYO phage cocktails from 1997 to 2014" submitted in October 2017 and currently under peer-revision. In this study, the compositions of 3 batches of a Georgian cocktail from 1997 to 2014 was compared by means of Next Generation Sequencing (NGS) and metagenomic analysis. Thirty and 29 phage draft genomes were found in the cocktails from 1997 and 2014, respectively. One of them was present in both sample and did not resemble any known phage genomes, strongly suggesting its novelty. Phage representatives of all bacterial targets supposedly targeted by the cocktail’s were found, as predicted using HostPhinder. A comparison between cocktails from 1997, 2000, and 2014 showed a closer composition between the first two cocktails. Chapter 4 presents the characterisation of historical S. aureus phages, once used for phage typing. Finally, the conclusive Chapter 5, recapitulates the main findings of this thesis and frame them into the perspective of potential future investigations.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Immunoinformatics and Machine Learning, Center for Biological Sequence Analysis, Department of Biotechnology and Biomedicine, Metabolic Signaling and Regulation
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Number of pages: 98
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Publisher: Technical University of Denmark (DTU)
Original language: English
Main Research Area: Technical/natural sciences
Linear peptidomimetics as potent antagonists of Staphylococcus aureus agr quorum sensing

Staphylococcus aureus is an important pathogen causing infections in humans and animals. Increasing problems with antimicrobial resistance has prompted the development of alternative treatment strategies, including antivirulence approaches targeting virulence regulation such as the agr quorum sensing system. agr is naturally induced by cyclic auto-inducing peptides (AIPs) binding to the AgrC receptor and cyclic peptide inhibitors have been identified competing with AIP binding to AgrC. Here, we disclose that small, linear peptidomimetics can act as specific and potent inhibitors of the S. aureus agr system via intercepting AIP-AgrC signal interaction at low micromolar concentrations. The corresponding linear peptide did not have this ability. This is the first report of a linear peptide-like molecule that interferes with agr activation by competitive binding to AgrC. Prospectively, these peptidomimetics may be valuable starting scaffolds for the development of new inhibitors of staphylococcal quorum sensing and virulence gene expression.
Localization and characterization of CYP76AE2 part of thapsigargin biosynthesis in Thapsia garganica

The Mediterranean plant *Thapsia garganica* (dicot, Apiaceae), also known as Deadly carrot, produces the highly toxic compound thapsigargin. This compound is a potent inhibitor of the SERCA calcium pump in mammals, and is of industrial importance as the active moiety of the anticancer drug Mipsagargin, currently in clinical trials. Knowledge of thapsigargin in planta storage and biosynthesis has so far been limited. Here we present the putative second step in thapsigargin biosynthesis, by showing that the cytochrome P450 TgCYP76AE2, transiently expressed in *Nicotiana benthamiana*, converts epikunzeaol into epidihydrocostunolide. Furthermore, we show that thapsigargin is likely to be stored in secretory ducts in the roots. Transcripts from TgTPS2 (epikunzeaol synthase) and TgCYP76AE2 in roots were only found in the epithelial cells lining these secretory ducts. This emphasizes the involvement of these cells in the biosynthesis of thapsigargin. This study paves the way for the further studies of thapsigargin biosynthesis.

**General information**

State: Accepted/In press

Organisations: Department of Biotechnology and Biomedicine, Natural Product Discovery, Photosynthetic Cell Factories, University of Copenhagen, University of Melbourne, Københavns Universitet, Aarhus University

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Locked nucleic acid: modality, diversity, and drug discovery

Over the past 20 years, the field of RNA-targeted therapeutics has advanced based on discoveries of modified oligonucleotide chemistries, and an ever-increasing understanding of how to apply cellular assays to identify oligonucleotides with pharmacological properties in vivo. Locked nucleic acid (LNA), which exhibits high binding affinity and potency, is widely used. Our understanding of RNA biology has also expanded tremendously, resulting in new approaches to engage RNA as a therapeutic target. Recent observations indicate that each oligonucleotide compound is a unique entity, and small structural differences between oligonucleotides can often lead to substantial differences in their pharmacological properties. Here, we outline new principles for drug discovery exploiting oligonucleotide diversity to identify rare molecules with unique pharmacological properties.

General information

State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Roche Innovation Center Copenhagen
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MARSI: metabolite analogues for rational strain improvement

Metabolite analogues (MAs) mimic the structure of native metabolites, can competitively inhibit their utilization in enzymatic reactions, and are commonly used as selection tools for isolating desirable mutants of industrial
microorganisms. Genome-scale metabolic models representing all biochemical reactions in an organism can be used to predict effects of MAs on cellular phenotypes. Here, we present the Metabolite Analogues for Rational Strain Improvement (MARSI) framework. MARSI provides a rational approach to strain improvement by searching for metabolites as targets instead of genes or reactions. The designs found by MARSI can be implemented by supplying MAs in the culture media, enabling metabolic rewiring without the use of recombinant DNA technologies that cannot always be used due to regulations. To facilitate experimental implementation, MARSI provides tools to identify candidate MAs to a target metabolite from a database of known drugs and analogues.
Metabolic mechanisms behind the type 2 diabetes susceptible phenotype in low birth weight individuals

**Background and aims:** Low birth weight (LBW) individuals have an increased risk of developing insulin resistance and type 2 diabetes compared with normal birth weight (NBW) individuals. Accordingly, young, healthy, LBW men of the study population examined in the present plasma metabolome studies show impaired hepatic insulin sensitivity and, in contrast to NBW men, develop impaired peripheral insulin sensitivity in response to a 5-day high-fat overfeeding. However, the metabolic mechanisms behind the type 2 diabetes susceptible phenotype in LBW individuals are not clear. Our primary aim of the present studies was to get novel insights into such mechanisms. LBW men of the present study population have lower pre-adipocyte mRNA expression levels of several differentiation markers, which may potentially lead to an impaired fatty acid storage capacity of these cells and a resulting increased fatty acid load to non-adipose tissue. Also, the LBW men display an increased fatty acid oxidation and a decreased glucose oxidation during both the isocaloric control diet and 5-day high-fat, high-calorie (HFHC) diet. Our specific aims of the present studies were to test the hypotheses that LBW men could have 1) an increased, incomplete fatty acid beta-oxidation in mitochondria, 2) an altered amino acid metabolism to ensure an adequate supply of tricarboxylic acid (TCA) cycle intermediates and thereby enable an efficient acetyl-CoA oxidation via the TCA cycle and an increased ketogenesis, respectively. Furthermore, LBW men have higher plasma C6-DC, C10-OH/C8-DC, and total hydroxyl-/dicarboxyl-acylcarnitine levels after the control diet, compared with NBW men, suggesting an increased fatty acid omega-oxidation in the endoplasmic reticulum of mainly the liver. Interestingly, the total hydroxyl-/dicarboxyl-acylcarnitine level was negatively associated with the fasting serum insulin level and hepatic insulin resistance after this diet. An increased omega-oxidation rate may therefore limit the amount of fatty acid substrates available for lipogenesis, including the synthesis of lipotoxic lipids such as ceramides and diacylglycerols that impair insulin signalling. In the second study, we demonstrated that LBW men had higher plasma alanine, proline, methionine, citrulline, and total amino acid levels after the HFHC diet compared with NBW men. The alanine level was negatively associated with the plasma C2 acylcarnitine level after this diet. A higher alanine level in the LBW men after the HFHC diet could therefore be accompanied by an increased anaplerotic formation of oxaloacetate to enable an efficient acetyl-CoA oxidation via the TCA cycle. Furthermore, the alanine and total amino acid levels tended to be negatively associated with the insulin-stimulated glucose uptake rate after the HFHC diet. Higher alanine and total amino acid levels in the LBW men after this diet could therefore be a consequence of their reduction in skeletal muscle insulin sensitivity due to high-fat overfeeding with a following increased skeletal muscle proteolysis and/or may potentially contribute to the impaired insulin sensitivity. Moreover, the alanine level was positively associated with the hepatic glucose production after the HFHC diet. A higher alanine level in the LBW men could therefore also be accompanied by an increased gluconeogenesis in the liver. In the third study, we found that LBW men did not show altered plasma ceramide levels after the control or HFHC diet compared with NBW men. An increased fatty acid oxidation rate in the LBW men during both diets may limit the amount of fatty acids available for de novo ceramide synthesis and thereby compensate for a likely increased fatty acid load to non-adipose tissue in these individuals.

**Methods:** Fasting plasma levels of 45 acylcarnitines, 15 amino acids, and 27 ceramides were measured in the young, healthy, LBW (≤ 10th percentile) and NBW (50-90th percentile) men of the above mentioned study population after the isocaloric control diet and 5-day HFHC (60 E % from fat, 50 % extra calories) diet intervention.

**Results and interpretations:** LBW men had higher plasma C2 and C4-OH acylcarnitine levels after the control diet, compared with NBW men, indicating an increased, incomplete fatty acid beta-oxidation in mitochondria with the limiting step at the acetyl-CoA oxidation via the TCA cycle and an increased ketogenesis, respectively. Furthermore, LBW men had higher plasma C6-DC, C10-OH/C8-DC, and total hydroxyl-/dicarboxyl-acylcarnitine levels after the control diet, compared with NBW men, suggesting an increased fatty acid omega-oxidation in the endoplasmic reticulum of mainly the liver. Interestingly, the total hydroxyl-/dicarboxyl-acylcarnitine level was negatively associated with the fasting serum insulin level and hepatic insulin resistance after this diet. An increased omega-oxidation rate may therefore limit the amount of fatty acid substrates available for lipogenesis, including the synthesis of lipotoxic lipids such as ceramides and diacylglycerols that impair insulin signalling. In the second study, we demonstrated that LBW men had higher plasma alanine, proline, methionine, citrulline, and total amino acid levels after the HFHC diet compared with NBW men. The alanine level was negatively associated with the plasma C2 acylcarnitine level after this diet. A higher alanine level in the LBW men after the HFHC diet could therefore be accompanied by an increased anaplerotic formation of oxaloacetate to enable an efficient acetyl-CoA oxidation via the TCA cycle. Furthermore, the alanine and total amino acid levels tended to be negatively associated with the insulin-stimulated glucose uptake rate after the HFHC diet. Higher alanine and total amino acid levels in the LBW men after this diet could therefore be a consequence of their reduction in skeletal muscle insulin sensitivity due to high-fat overfeeding with a following increased skeletal muscle proteolysis and/or may potentially contribute to the impaired insulin sensitivity. Moreover, the alanine level was positively associated with the hepatic glucose production after the HFHC diet. A higher alanine level in the LBW men could therefore also be accompanied by an increased gluconeogenesis in the liver. In the third study, we found that LBW men did not show altered plasma ceramide levels after the control or HFHC diet compared with NBW men. An increased fatty acid oxidation rate in the LBW men during both diets may limit the amount of fatty acids available for de novo ceramide synthesis and thereby compensate for a likely increased fatty acid load to non-adipose tissue in these individuals.

**Conclusions:** LBW men showed alterations in fasting plasma acylcarnitine and amino acid levels after the isocaloric control diet and 5-day HFHC diet, respectively, that have been described to be associated with insulin resistance and type 2 diabetes. Additional plasma and tissue metabolome studies in LBW and NBW individuals, as well as supplementary
functional studies, are needed to further explain the metabolic events leading to the altered plasma metabolite profiles in LBW men, and moreover to determine the extent to which these events may be part of the type 2 diabetes susceptible phenotype in LBW individuals.

**General information**

State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology
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**Relations**

Projects:
Metabolic mechanisms behind the type 2 diabetes susceptible phenotype in low birth weight individuals

Publication: Research › Ph.D. thesis – Annual report year: 2018

**Metabolite production by species of Stemphylium**

Morphology and phylogeny has been used to distinguish members of the plant pathogenic fungal genus Stemphylium. A third method for distinguishing species is by chemotaxonomy. The main goal of the present study was to investigate the chemical potential of Stemphylium via HPLC-UV-MS analysis, while also exploring the potential of chemotaxonomy as a robust identification method for Stemphylium. Several species were found to have species-specific metabolites, while other species were distinguishable by a broader metabolic profile rather than specific metabolites. Many previously described metabolites were found to be important for distinguishing species, while some unknown metabolites were also found to have important roles in distinguishing species of Stemphylium. This study is the first of its kind to investigate the chemical potential of Stemphylium across the whole genus.

**General information**

State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, Natural Product Discovery, Fungal Degradation, Oregon State University
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Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.075 SNIP 1.103 CiteScore 2.56
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Method for reducing ammonium and lactate production in cho cells

The present invention relates to modified producer cells for improved production of therapeutic proteins. Specifically, the inventors have found that removing genes involved in amino acid catabolism in Chinese Hamster Ovary (CHO) cells improves the cell growth and viability and likely also the yield of a recombinant therapeutic protein produced by the cells.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Quantitative Modeling of Cell Metabolism, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Ley, D. (Intern), Andersen, M. R. (Intern), Kiltegaard, H. F. (Intern)
Publication date: 2018

Publication information
Diesel fuel is one of the most important sources of hydrocarbon contamination worldwide. Its composition consists of a complex mixture of n-alkanes, branched alkanes and aromatic compounds. Hydrocarbon degradation in Pseudomonas species has been mostly studied under aerobic conditions; however, a dynamic spectrum of oxygen availability can be found in the environment. Pseudomonas extremaustralis, an Antarctic bacterium isolated from a pristine environment, is able to degrade diesel fuel and presents a wide microaerophilic metabolism. In this work RNA-deep sequence experiments were analyzed comparing the expression profile in aerobic and microaerophilic cultures. Interestingly, genes involved in alkane degradation, including alkB, were over-expressed in micro-aerobiosis in absence of hydrocarbon compounds. In minimal media supplemented with diesel fuel, n-alkanes degradation (C13-C19) after 7 days was observed under low oxygen conditions but not in aerobiosis. In-silico analysis of the alkB promoter zone showed a putative binding sequence for the anaerobic global regulator, Anr. Our results indicate that some diesel fuel components can be utilized as sole carbon source under microaerophilic conditions for cell maintenance or slow growth in a Pseudomonas species and this metabolism could represent an adaptive advantage in polluted environments.
Modelling the influence of metabolite diffusion on non-starter lactic acid bacteria growth in ripening Cheddar cheese

The influence of metabolite diffusion within the cheese matrix on growth of non-starter lactic acid bacteria (NSLAB) during Cheddar cheese ripening was mathematically modelled. The model was calibrated at a realistic range of diffusion of metabolites and the decay and growth parameters of immobilised starter LAB (SLAB) and NSLAB colonies, respectively. Metabolite diffusion is the limiting factor for NSLAB growth only if essential metabolite molecules are extremely large or otherwise immobilised in the matrix. For relatively small molecules diffusion cannot be a limiting factor; the diffusive replenishment of small molecule nutrients around the NSLAB colonies consuming them is generally faster than the release rate from all possible sources within the curd. Assuming that the only nutrient source limiting NSLAB growth is the release of metabolites from lysed SLAB colonies, the decay rate of SLAB, rather than metabolite diffusion, most probably determines the rate of NSLAB growth during Cheddar cheese ripening.

General information
State: Accepted/In press
Organisations: Department of Biotechnology and Biomedicine, University of Copenhagen
Authors: Czárán, T. (Ekstern), Rattray, F. P. (Ekstern), Møller, C. O. A. (Ekstern), Christensen, B. B. (Intern)
Number of pages: 36
Publication date: 2018
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Necrotizing enterocolitis is associated with acute brain responses in preterm pigs

BACKGROUND: Necrotizing enterocolitis (NEC) is an acute gut inflammatory disorder that occurs in preterm infants in the first weeks after birth. Infants surviving NEC often show impaired neurodevelopment. The mechanisms linking NEC lesions with later neurodevelopment are poorly understood but may include proinflammatory signaling in the immature brain. Using preterm pigs as a model for preterm infants, we hypothesized that severe intestinal NEC lesions are associated with acute effects on the developing hippocampus. METHODS: Cesarean-delivered preterm pigs (n=117) were reared for 8 days and spontaneously developed variable severity of NEC lesions. Neonatal arousal, physical activity, and in vitro neuritogenic effects of cerebrospinal fluid (CSF) were investigated in pigs showing NEC lesions in the colon (Co-NEC) or in the small intestine (SI-NEC). Hippocampal transcriptome analysis and qPCR were used to assess gene expressions and their relation to biological processes, including neuroinflammation, and neural plasticity. Microglia activation was quantified by stereology. The neuritogenic response to selected proteins was investigated in primary cultures of hippocampal neurons. RESULTS: NEC development rapidly reduced the physical activity of pigs, especially...
when lesions occurred in the small intestine. Si-NEC and Co-NEC were associated with 27 and 12 hippocampal
differentially expressed genes (DEGs), respectively. These included genes related to neuroinflammation (i.e., S100A8,
S100A9, IL8, IL6, MMP8, SAA, TAGLN2) and hypoxia (i.e., PDK4, IER3, TXNIP, AGER), and they were all upregulated in
Si-NEC pigs. Genes related to protection against oxidative stress (HBB, ALAS2) and oligodendrocytes (OPALIN) were
downregulated in Si-NEC pigs. CSF collected from NEC pigs promoted neurite outgrowth in vitro, and the S100A9 and
S100A8/S100A9 proteins may mediate the neuritogenic effects of NEC-related CSF on hippocampal neurons. NEC
lesions did not affect total microglial cell number but markedly increased the proportion of Iba1-positive amoeboid
microglial cells. CONCLUSIONS: NEC lesions, especially when present in the small intestine, are associated with changes to hippocampal gene expression that potentially mediate neuroinflammation and disturbed neural circuit formation via enhanced neuronal differentiation. Early brain-protective interventions may be critical for preterm infants affected by intestinal NEC lesions to reduce their later neurological dysfunctions.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, National Veterinary Institute, Innate Immunology,
University of Copenhagen, Bispebjerg-Frederiksberg Hospitals, Chinese Academy of Agricultural Sciences
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Chatterton, D. E. W. (Ekstern), Kaalund, S. S. (Ekstern), Gao, F. (Ekstern), Sangild, P. T. (Ekstern), Pankratova, S.
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Publication date: 2018
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**New Penicillium and Talaromyces species from honey, pollen and nests of stingless bees**

*Penicillium* and *Talaromyces* species have a worldwide distribution and are isolated from various materials and hosts,
including insects and their substrates. The aim of this study was to characterize the *Penicillium* and *Talaromyces* species
obtained during a survey of honey, pollen and the inside of nests of *Melipona scutellaris*. A total of 100 isolates were
obtained during the survey and 82% of those strains belonged to *Penicillium* and 18% to *Talaromyces*. Identification of
these isolates was performed based on phenotypic characters and ß-tubulin and ITS sequencing. Twenty-one species
were identified in *Penicillium* and six in *Talaromyces*, including seven new species. These new species were studied in
detail using a polyphasic approach combining phenotypic, molecular and extrolite data. The four new *Penicillium* species
belong to sections *Sclerotiora* (*Penicillium fernandesiae* sp. nov., *Penicillium mellis* sp. nov., *Penicillium meliponae* sp.
nov.) and *Gracilenta* (*Penicillium apimei* sp. nov.) and the three new *Talaromyces* species to sections *Helici* (*Talaromyces
pigmenlosus* sp. nov.), *Talaromyces* (*Talaromyces mycothecae* sp. nov.) and *Trachysperm* (*Talaromyces brasiliensis* sp.
nov.). The invalidly described species *Penicillium echinulonalgiovense* sp. nov. was also isolated during the survey and
this species is validated here.
Occurrence of Aspergillus section Flavi and aflatoxins in Brazilian rice: From field to market

The guarantee of the high quality of rice is of utmost importance because any toxic contaminant may affect consumer health, especially in countries such as Brazil where rice is part of the daily diet. A total of 187 rice samples, from field, processing and market from two different production systems, wetland from the state of Rio Grande do Sul, dryland, from the state of Maranhão and market samples from the state of São Paulo, were analyzed for fungi belonging to Aspergillus section Flavi and the presence of aflatoxins. Twenty-three soil samples from wetland and dryland were also analyzed. A total of 383 Aspergillus section Flavi strains were isolated from rice and soil samples. Using a polyphasic approach, with phenotypic (morphology and extrolite profiles) and molecular data (beta-tubulin gene sequences), five species were identified: A. flavus, A. caelatus, A. novoparasiticus, A. arachidicola and A. pseudocaelatus. This is the first report of these last three species from rice and rice plantation soil. Only seven (17%) of the A. flavus isolates produced type B aflatoxins, but 95% produced kojic acid and 69% cyclopiazonic acid. Less than 14% of the rice samples were contaminated with aflatoxins, but two of the market samples were well above the maximum tolerable limit (5 μg/kg), established by the Brazilian National Health Surveillance Agency.
On the biosynthetic origin of carminic acid

The chemical composition of the scale insect Dactylopius coccus was analyzed with the aim to discover new possible intermediates in the biosynthesis of carminic acid. UPLC-DAD/HRMS analyses of fresh and dried insects resulted in the identification of three novel carminic acid analogues and the verification of several previously described intermediates. Structural elucidation revealed that the three novel compounds were desoxyerythrolaccin-O-glucosyl (DE-O-Glcp), 5,6-didehydroxyerythrolaccin 3-O-β-D-glucopyranoside (DDE-3-O-Glcp), and flavokermesic acid anthrone (FKA). The finding of FKA in D. coccus provides solid evidence of a polyketide, rather than a shikimate, origin of coccid pigments. Based on the newly identified compounds, we present a detailed biosynthetic scheme that accounts for the formation of carminic acid (CA) in D. coccus and all described coccid pigments which share a flavokermesic acid (FK) core. Detection of coccid pigment intermediates in members of the Planococcus (mealybugs) and Pseudaulacaspis genera shows that the ability to form these pigments is taxonomically more widely spread than previously documented. The shared core-FK-biosynthetic pathway and wider taxonomic distribution suggests a common evolutionary origin for the trait in all coccid dye producing insect species.
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Organisations: Department of Biotechnology and Biomedicine, Department of Chemistry, Organic Chemistry, Eukaryotic Molecular Cell Biology, Natural Product Discovery, Biosynthetic Pathway Engineering, University of Copenhagen, Chr. Hansen AS
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Web of Science (2017): Indexed Yes
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BFI (2015): BFI-level 1
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.624 SNIP 1.215 CiteScore 3.59
Web of Science (2014): Indexed yes
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Scopus rating (2013): SJR 1.705 SNIP 1.349 CiteScore 3.87
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Scopus rating (2012): SJR 1.628 SNIP 1.209 CiteScore 3.56
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.712 SNIP 1.298 CiteScore 3.54
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.757 SNIP 1.302
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.585 SNIP 1.008
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.312 SNIP 1.029
Scopus rating (2007): SJR 1.608 SNIP 1.146
Scopus rating (2006): SJR 1.439 SNIP 1.017
Scopus rating (2005): SJR 1.449 SNIP 1.062
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.383 SNIP 1.003
Scopus rating (2003): SJR 1.468 SNIP 1.116
Scopus rating (2002): SJR 1.232 SNIP 1.128
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.935 SNIP 1.002
Scopus rating (2000): SJR 1.392 SNIP 1.051
Scopus rating (1999): SJR 1.326 SNIP 1.039
Pyocyanin is a toxin produced by Pseudomonas aeruginosa. Here we describe a novel paper-based electrochemical sensor for pyocyanin detection, manufactured with a simple and inexpensive approach based on electrode printing on paper. The resulting sensors constitute an effective electrochemical method to quantify pyocyanin in bacterial cultures without the conventional time consuming pretreatment of the samples. The electrochemical properties of the paper-based sensors were evaluated by ferri/ferrocyanide as a redox mediator, and showed reliable sensing performance. The paper-based sensors readily allow for the determination of pyocyanin in bacterial cultures with high reproducibility, achieving a limit of detection of 95 nM and a sensitivity of 4.30 μA/μM in standard culture media. Compared to the similar commercial ceramic based sensors, it is a 2.3-fold enhanced performance. The simple in-house fabrication of sensors for pyocyanin quantification allows researchers to understand in vitro adaptation of P. aeruginosa infections via rapid screenings of bacterial cultures that otherwise are expensive and time-consuming.

General information
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Organisations: Department of Biotechnology and Biomedicine, Department of Micro- and Nanotechnology, Nano Bio Integrated Systems, Infection Microbiology, Novo Nordisk Foundation Center for Biosustainability, Department of Applied Mathematics and Computer Science, Embedded Systems Engineering, Copenhagen Center for Health Technology, Roskilde University, University of Copenhagen
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Web of Science (2017): Indexed yes
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
**Parts Characterization for Tunable Protein Expression**

Flow-seq combines flexible genome engineering methods with flow cytometry-based cell sorting and deep DNA sequencing to enable comprehensive interrogation of genotype to phenotype relationships. One application is to study the effect of specific regulatory elements on protein expression. Constructing targeted genomic variation around genomically integrated fluorescent marker genes enables rapid elucidation of the contribution of specific sequence variants to protein expression. Such an approach can be used to characterize the impact of modifications to the Shine-Dalgarno sequence in *Escherichia coli*.

**General information**

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Department of Biotechnology and Biomedicine
Authors: Klausen, M. S. (Intern), Sommer, M. O. A. (Intern)
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Series: Methods in Molecular Biology
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Flow cytometry cell sorting, Flow-seq, Next-generation sequencing, Shine-Dalgarno sequence

**Phylogenetic distribution of roseobacticides in the *Roseobacter* group and their effect on microalgae**

The *Roseobacter*-group species *Phaeobacter inhibens* produces the antibacterial tropodithietic acid (TDA) and the algaecidal roseobacticides with both compound classes sharing part of the same biosynthetic pathway. The purpose of this study was to investigate the production of roseobacticides more broadly in TDA-producing roseobacters and to
compare the effect of producers and non-producers on microalgae. Of 33 roseobacters analyzed, roseobacticide production was a unique feature of TDA-producing *P. inhibens*, *P. gallaeciensis* and *P. piscinae* strains. One TDA-producing *Phaeobacter*, 27-4, did not produce roseobacticides, possibly due to a transposable element. TDA-producing *Ruegeria* and *Pseudovibrio* did not produce roseobacticides. Addition of roseobacticide-containing bacterial extracts affected the growth of the microalgae *Rhodomonas salina*, *Thalassiosira pseudonana* and *Emiliania huxleyi*, while growth of *Tetraselmis suecica* was unaffected. During co-cultivation, growth of *E. huxleyi* was initially stimulated by the roseobacticide producer DSM 17395, while the subsequent decline in algal cell numbers during senescence was enhanced. Strain 27-4 that does not produce roseobacticides had no effect on algal growth. Both bacterial strains, DSM 17395 and 27-4, grew during co-cultivation presumably utilizing algal exudates. Furthermore, TDA-producing roseobacters have potential as probiotics in marine larviculture and it is promising that the live feed *Tetraselmis* was unaffected by roseobacticides-containing extracts.
genes in pigs affected by orthopedic surgery and compare it to the expression in humans and mice as mice, are one of the most applied animal species in orthopedics today. In the present study, the local molecular response to drilling of a tibial implant cavity, and the subsequent insertion of a steel implant was examined in a porcine model. Pigs were euthanized five days after drilling of the bone. The molecular response of 73 different genes was analyzed using a high-throughput quantitative polymerase chain reaction platform and compared to histopathology. Histologically, it was found that bone remodeling was initiated on day 5 after surgery and was associated with upregulation of several genes involved in bone degradation and formation (CTSK, ACP5, IBSP, RANK, RANKL and COL1A1). Interleukin-6 and several acute-phase proteins (C3, SAA and ITIH4) were significantly upregulated, indicating their importance in the initial process of healing and osseointegration. All tested bone morphogenic proteins (BMP2, -4 and -7) including their inhibitor noggin were also significantly upregulated. Surprisingly, vascular endothelial growth factor A was not found to be regulated five days after surgery while several other vascular growth factors (ANGPT1, ANGPT2 and PTN) were upregulated. The pig was found to be a useful model for elucidation of bone regulatory genes in humans.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, National Veterinary Institute, Innate Immunology, University of Copenhagen
Authors: Lüthje, F. L. (Intern), Skovgaard, K. (Intern), Jensen, H. E. (Ekstern), Kruse Jensen, L. (Ekstern)
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- Scopus rating (2017): SNIP 0.884 SJR 0.665
- Web of Science (2017): Indexed Yes
- BFI (2016): BFI-level 1
- Scopus rating (2016): CiteScore 1.36 SJR 0.744 SNIP 0.798
- BFI (2015): BFI-level 1
- Scopus rating (2015): SJR 0.635 SNIP 0.696 CiteScore 1.35
- BFI (2014): BFI-level 1
- Scopus rating (2014): SJR 0.538 SNIP 0.78 CiteScore 1.13
- BFI (2013): BFI-level 1
- Scopus rating (2013): SJR 0.39 SNIP 0.555 CiteScore 0.95
- ISI indexed (2013): ISI indexed yes
- BFI (2012): BFI-level 1
- Scopus rating (2012): SJR 0.528 SNIP 0.777 CiteScore 1.32
- ISI indexed (2012): ISI indexed yes
- BFI (2011): BFI-level 1
- Scopus rating (2011): SJR 0.509 SNIP 0.708 CiteScore 1.25
- ISI indexed (2011): ISI indexed yes
- Web of Science (2011): Indexed yes
- BFI (2010): BFI-level 1
- Scopus rating (2010): SJR 0.564 SNIP 0.808
- BFI (2009): BFI-level 1
- Scopus rating (2009): SJR 0.584 SNIP 1.029
- BFI (2008): BFI-level 1
- Scopus rating (2008): SJR 0.404 SNIP 0.755
- Scopus rating (2007): SJR 0.356 SNIP 0.681
- Scopus rating (2006): SJR 0.403 SNIP 0.709
- Scopus rating (2005): SJR 0.652 SNIP 0.985
- Web of Science (2005): Indexed yes
- Scopus rating (2004): SJR 0.61 SNIP 1.361
Plasma ceramide levels are altered in low and normal birth weight men in response to short-term high-fat overfeeding

Low birth weight (LBW) individuals have an increased risk of developing insulin resistance and type 2 diabetes compared with normal birth weight (NBW) individuals. We hypothesised that LBW individuals exhibit an increased fatty acid flux into lipogenesis in non-adipose tissue with a resulting accumulation of lipotoxic lipids, including ceramides, in the blood. Therefore, we measured fasting plasma levels of 27 ceramides in 18 young, healthy, LBW men and 25 NBW controls after an isocaloric control diet and a 5-day high-fat, high-calorie diet by HPLC-HRMS. LBW men did not show elevated plasma ceramide levels after the control or high-fat, high-calorie diet. An increased fatty acid oxidation rate in these individuals during both diets may limit ceramide synthesis and thereby compensate for a likely increased fatty acid load to non-adipose tissue. Interestingly, LBW and NBW men decreased d18:0–18:1/d18:1–18:0 and d18:1–24:2/d18:2–24:1 levels and increased the d18:0–24:1a level in response to overfeeding. Plasma d18:0–24:1a and total ceramide levels were positively associated with the fasting blood glucose level and endogenous glucose production after the control diet, and the total ceramide level was in addition positively associated with hepatic insulin resistance. Further studies are needed to determine if lipotoxicity contributes to insulin resistance in LBW individuals.
Polyphasic data support the splitting of *Aspergillus candidus* into two species; proposal of *Aspergillus dobrogensis* sp. nov. *Aspergillus candidus* is a species frequently isolated from stored grain, food, indoor environments, soil and occasionally also from clinical material. Recent bioprospecting studies highlighted the potential of using *A. candidus* and its relatives in various industrial sectors as a result of their significant production of enzymes and bioactive compounds. A high genetic variability was observed among *A. candidus* isolates originating from various European countries and the USA, that were mostly isolated from indoor environments, caves and clinical material. The *A. candidus sensu lato* isolates were characterized by DNA sequencing of four genetic loci, and agreement between molecular species delimitation results, morphological characters and exometabolite spectra were studied. Classical phylogenetic methods (maximum likelihood, Bayesian inference) and species delimitation methods based on the multispecies coalescent model supported recognition of up to three species in *A. candidus sensu lato*. After evaluation of phenotypic data, a broader species concept was adopted, and only one new species, *Aspergillus dobrogensis*, was proposed. This species is represented by 22 strains originating from seven countries (ex-type strain CCF 4651 =NRRL 62821 =IBT 32697 =CBS 143370) and its differentiation from *A. candidus* is relevant for bioprospecting studies because these species have different exometabolite profiles. Evaluation of the antifungal susceptibility of section *Candidi* members to six antifungals using the reference EUCAST method showed that all species have low minimum inhibitory concentrations for all tested antifungals. These results suggest applicability of a wide spectrum of antifungal agents for treatment of infections caused by species from section *Candidi*.

**General information**

**State:** Published  
**Organisations:** Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Czech Academy of Sciences, Charles University, Statens Serum Institute, Universitat Rovira i Virgili, EMSL Analytical, Inc., Westerdijk Fungal Biodiversity Institute, Statens Serum Institut, Faculdade de Medicina de Sao Jose do Rio Preto  
**Authors:** Hubka, V. (Ekstern), Nováková, A. (Ekstern), Jurjević, Ž. (Ekstern), Sklenář, F. (Ekstern), Frisvad, J. C. (Intern), Houbraken, J. (Ekstern), Arendrup, M. C. (Ekstern), Jørgensen, K. M. (Forskerdatabase), Siqueira, J. P. (Ekstern), Gené, J. (Ekstern), Kolarík, M. (Ekstern)  
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**Scopus rating (2016):** CiteScore 2.22 SJR 0.892 SNIP 1.164  
**Web of Science (2016):** Indexed yes  
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**Scopus rating (2015):** SJR 1.098 SNIP 1.484 CiteScore 2.74  
**Web of Science (2015):** Indexed yes
Antibody technologies are being increasingly applied in the field of toxinology. Fuelled by the many advances in immunology, synthetic biology, and antibody research, different approaches and antibody formats are being investigated for the ability to neutralize animal toxins. These different molecular formats each have their own therapeutic characteristics. In this review, we provide an overview of the advances made in the development of toxin-targeting antibodies, and discuss the benefits and drawbacks of different antibody formats in relation to their ability to neutralize toxins, pharmacokinetic features, propensity to cause adverse reactions, formulation, and expression for research and development (R&D) purposes and large-scale manufacturing. A research trend seems to be emerging towards the use of human antibody formats as well as camelid heavy-domain antibody fragments due to their compatibility with the human immune system, beneficial therapeutic properties, and the ability to manufacture these molecules cost-effectively.
Pseudoalteromonas haloplanktis TAC125 produces 4-hydroxybenzoic acid that induces pyroptosis in human A459 lung adenocarcinoma cells

In order to exploit the rich reservoir of marine cold-adapted bacteria as a source of bioactive metabolites, ethyl acetate crude extracts of thirteen polar marine bacteria were tested for their antiproliferative activity on A549 lung epithelial cancer cells. The crude extract from Pseudoalteromonas haloplanktis TAC125 was the most active in inhibiting cell proliferation. Extensive bioassay-guided purification and mass spectrometric characterization allowed the identification of 4-hydroxybenzoic acid (4-HBA) as the molecule responsible for this bioactivity. We further demonstrate that 4-HBA inhibits A549 cancer cell proliferation with an IC50 value...
Recognition of microbial viability via TLR8 drives $T_{FH}$ cell differentiation and vaccine responses

Live attenuated vaccines are generally highly efficacious and often superior to inactivated vaccines, yet the underlying mechanisms of this remain largely unclear. Here we identify recognition of microbial viability as a potent stimulus for follicular helper T cell ($T_{FH}$ cell) differentiation and vaccine responses. Antigen-presenting cells (APCs) distinguished viable bacteria from dead bacteria through Toll-like receptor 8 (TLR8)-dependent detection of bacterial RNA. In contrast to dead bacteria and other TLR ligands, live bacteria, bacterial RNA and synthetic TLR8 agonists induced a specific cytokine profile in human and porcine APCs, thereby promoting $T_{FH}$ cell differentiation. In domestic pigs, immunization with a live bacterial vaccine induced robust $T_{FH}$ cell and antibody responses, but immunization with its heat-killed counterpart did not. Finally, a hypermorphic TLR8 polymorphism was associated with protective immunity elicited by vaccination with bacillus Calmette-Guérin (BCG) in a human cohort. We have thus identified TLR8 as an important driver of $T_{FH}$ cell differentiation and a promising target for $T_{FH}$ cell-skewing vaccine adjuvants.

General information

State: Published
Organisations: Department of Biotechnology and Biomedicine, National Veterinary Institute, Adaptive Immunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Leibniz Institute, Federal Research Institute for Animal Health, Osmania University, University of Southern Denmark, Leibniz Institute, Wageningen University
Authors: Ugolini, M. (Ekstern), Gerhard, J. (Ekstern), Burkert, S. (Ekstern), Jensen, K. J. (Intern), Georg, P. (Ekstern), Ebner, F. (Ekstern), Volkers, S. M. (Ekstern), Thada, S. (Ekstern), Dietert, K. (Ekstern), Bauer, L. (Ekstern), Schäfer, A. (Ekstern), Helbig, E. T. (Ekstern), Opitz, B. (Ekstern), Kurth, F. (Ekstern), Sur, S. (Ekstern), Dittrich, N. (Ekstern), Gaddam, S. (Ekstern), Conrad, M. L. (Ekstern), Benn, C. S. (Ekstern), Blohm, U. (Ekstern), Gruber, A. D. (Ekstern), Hutloff, A. (Ekstern), Hartmann, S. (Ekstern), Boekschoten, M. V. (Ekstern), Müller, M. (Ekstern), Jungersen, G. (Intern), Schumann, R. R. (Ekstern), Suttrop, N. (Ekstern), Sander, L. E. (Ekstern)
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Scopus rating (2017): SNIP 4.019 SJR 14.007
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Reconstructing Dynamic Promoter Activity Profiles from Reporter Gene Data

Accurate characterization of promoter activity is important when designing expression systems for systems biology and metabolic engineering applications. Promoters that respond to changes in the environment enable the dynamic control of gene expression without the necessity of inducer compounds, for example. However, the dynamic nature of these processes poses challenges for estimating promoter activity. Most experimental approaches utilize reporter gene expression to estimate promoter activity. Typically the reporter gene encodes a fluorescent protein that is used to infer a constant promoter activity despite the fact that the observed output may be dynamic and is a number of steps away from the transcription process. In fact, some promoters that are often thought of as constitutive can show changes in activity when growth conditions change. For these reasons, we have developed a system of ordinary differential equations for estimating dynamic promoter activity for promoters that change their activity in response to the environment that is robust to noise and changes in growth rate. Our approach, inference of dynamic promoter activity (PromAct), improves on existing methods by more accurately inferring known promoter activity profiles. This method is also capable of estimating the correct scale of promoter activity and can be applied to quantitative data sets to estimate quantitative rates.

General information
State: Published
Organisations: Department of Electrical Engineering, Biomedical Engineering, Novo Nordisk Foundation Center for Biosustainability, iLoop, Department of Biotechnology and Biomedicine, Regulatory Genomics, Technical University of Denmark
Authors: Kannan, S. (Ekstern), Sams, T. (Intern), Maury, J. (Intern), Workman, C. T. (Intern)
Publication: Research - peer-review › Journal article – Annual report year: 2018
Revealing the Dimeric Crystal and Solution Structure of β-Lactoglobulin at pH 4 and Its pH and Salt Dependent Monomer–Dimer Equilibrium

The dimeric structure of bovine β-lactoglobulin A (BLGA) at pH 4.0 was solved to 2.0 Å resolution. Fitting the BLGA pH 4.0 structure to SAXS data at low ionic strength (goodness of fit R-factor = 3.6%) verified the dimeric state in solution. Analysis of the monomer–dimer equilibrium at varying pH and ionic strength by SAXS and scattering modeling showed that BLGA is dimeric at pH 3.0 and 4.0, shifting toward a monomer at pH 2.2, 2.6, and 7.0 yielding monomer/dimer ratios of 80/20%, 50/50%, and 25/75%, respectively. BLGA remained a dimer at pH 3.0 and 4.0 in 50–150 mM NaCl, whereas the electrostatic shielding raised the dimer content at pH 2.2, 2.6, and 7.0, i.e., below and above the pI. Overall, the findings provide new insights into the molecular characteristics of BLGA relevant for dairy product formulations and for various biotechnological and pharmaceutical applications.
Serine/Threonine protein kinases from bacteria, archaea and eukarya share a common evolutionary origin deeply rooted in the tree of life

The main family of serine/threonine/tyrosine protein kinases present in eukarya was defined and described by Hanks et al. in 1988. It was initially believed that these kinases do not exist in bacteria, but extensive genome sequencing revealed their existence in many bacteria. For historical reasons, the term "eukaryotic-type kinases" propagated in the literature to describe bacterial members of this protein family. Here, we argue that this term should be abandoned as a misnomer, and we provide several lines of evidence to support this claim. Our comprehensive phylostratigraphic analysis suggests that Hanks-type kinases present in eukarya, bacteria and archaea all share a common evolutionary origin in the lineage...
leading to the last universal common ancestor (LUCA). We found no evidence to suggest substantial horizontal transfer of genes encoding Hanks-type kinases from eukarya to bacteria. Moreover, our systematic structural comparison suggests that bacterial Hanks-type kinases resemble their eukaryal counterparts very closely, while their structures appear to be dissimilar from other kinase families of bacterial origin. This indicates that a convergent evolution scenario, by which bacterial kinases could have evolved a kinase domain similar to that of eukaryal Hanks-type kinases, is not very likely. Overall, our results strongly support a monophyletic origin of all Hanks-type kinases, and we therefore propose that this term should be adopted as a universal name for this protein family.

**General information**

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, Bacterial Signal Transduction, Department of Biotechnology and Biomedicine, Infection Microbiology, University of Zagreb, Ruder Boskovic Institute, Chalmers University of Technology
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  - BFI (2016): BFI-level 1
  - Scopus rating (2016): CiteScore 4.13 SJR 3.377 SNIP 1.162
  - BFI (2015): BFI-level 1
  - Scopus rating (2015): SJR 3.005 SNIP 1.099 CiteScore 3.97
  - Web of Science (2015): Indexed yes
  - BFI (2014): BFI-level 1
  - Scopus rating (2014): SJR 2.823 SNIP 1.111 CiteScore 3.7
  - BFI (2013): BFI-level 1
  - Scopus rating (2013): SJR 3.145 SNIP 1.09 CiteScore 3.92
  - ISI indexed (2013): ISI indexed yes
  - BFI (2012): BFI-level 1
  - Scopus rating (2012): SJR 3.034 SNIP 1.136 CiteScore 3.91
  - ISI indexed (2012): ISI indexed yes
  - BFI (2011): BFI-level 1
  - Scopus rating (2011): SJR 3.142 SNIP 1.19 CiteScore 4.01
  - ISI indexed (2011): ISI indexed yes
  - Web of Science (2011): Indexed yes
  - BFI (2010): BFI-level 1
  - Scopus rating (2010): SJR 3.169 SNIP 1.156
  - Web of Science (2010): Indexed yes
  - BFI (2009): BFI-level 1
  - Scopus rating (2009): SJR 3.512 SNIP 1.157
  - Web of Science (2009): Indexed yes
  - BFI (2008): BFI-level 2
  - Web of Science (2008): Indexed yes
  - Scopus rating (2007): SJR 3.857 SNIP 1.284
  - Web of Science (2007): Indexed yes
Various fungi of the genera Aspergillus, Penicillium, and Malbranchea produce prenylated indole alkaloids possessing a bicyclo[2.2.2]diazaoctane ring system. After the discovery of distinct enantiomers of the natural alkaloids stephacidin A and notoamide B, from A. protuberus MF297-2 and A. amoenum NRRL 35660, another fungi, A. taichungensis, was found to produce their diastereomers, 6-epi-stephacidin A and versicolamide B, as major metabolites. Distinct enantiomers of stephacidin A and 6-epi-stephacidin A may be derived from a common precursor, notoamide S, by enzymes that form a bicyclo[2.2.2]diazaoctane core via a putative intramolecular hetero-Diels-Alder cycloaddition. This review provides our current understanding of the structural and stereochemical homologies and disparities of these alkaloids. Through the deployment of biomimetic syntheses, whole-genome sequencing, and biochemical studies, a unified biogenesis of both the dioxopiperazine and the monooxopiperazine families of prenylated indole alkaloids constituted of bicyclo[2.2.2]diazaoctane ring systems is presented.
Structure dependent antioxidant capacity of phlorotannins from Icelandic Fucus vesiculosus by UHPLC-DAD-ECD-QTOFMS

Brown algae are rich in polyphenolic compounds, phlorotannins, which have been found to possess high in vitro antioxidant capacity, especially DPPH radical scavenging activity, due to the high number of hydroxyl groups. Whereas, the overall antioxidant capacity of brown algae extracts has been widely studied, the antioxidant capacity of individual phlorotannins has been rarely explored. The aim of this study was to determine the structure dependant antioxidant capacity of phlorotannins from Icelandic brown algae, Fucus vesiculosus. The antioxidant capacity of individual phlorotannins was determined by an on-line method using liquid chromatography and an electrochemical detector followed by quadrupole Time of Flight mass spectrometry (UHPLC-DAD-ECD-QTOFMS). Tentative structural elucidation of 13 phlorotannin isomers from EAF was obtained by LC-DAD-QTOFMS, ranging from 374 to 870 Da. On-line determination of antioxidant capacity of the individual phlorotannins generally showed that low molecular phlorotannins exhibited higher antioxidant capacity and that the capacity decreased with polymerisation.

General information
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Organisations: National Food Institute, Research Group for Bioactives – Analysis and Application, Department of Biotechnology and Biomedicine, DTU Metabolomics Core, Lund University, Matís ltd.
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Subtyping of Swine Influenza Viruses Using a High-Throughput Real-Time PCR Platform

Influenza A viruses (IAVs) are important human and animal pathogens with high impact on human and animal health. In Denmark, a passive surveillance program for IAV in pigs has been performed since 2011, where screening tests and subsequent subtyping are performed by reverse transcription quantitative real-time PCR (RT-qPCR). A disadvantage of the current subtyping system is that several assays are needed to cover the wide range of circulating subtypes, which makes the system expensive and time-consuming. Therefore, the aim of the present study was to develop a high-throughput method, which could improve surveillance of swine influenza viruses (swIAVs) and lower the costs of virus subtyping. Twelve qPCR assays specific for various hemagglutinin and neuraminidase gene lineages relevant for swIAV and six assays specific for the internal genes of IAV were developed and optimized for the high-throughput qPCR platform BioMark (Fluidigm). The qPCR assays were validated and optimized to run under the same reaction conditions using a 48.48 dynamic array (48.48DA). The sensitivity and specificity was assessed by testing virus isolates and field samples with known subtypes. The results revealed a performance of the swIAV 48.48DA similar to conventional real-time analysis, and furthermore, the specificity of swIAV 48.48DA was very high and without cross reactions between the assays. This high-throughput system provides a cost-effective alternative for subtyping of swIAVs.

General information
State: Published
Organisations: National Veterinary Institute, Virology, Department of Biotechnology and Biomedicine, Innate Immunology, Friedrich Loeffler Institute
Authors: Goecke, N. B. (Intern), Krogh, J. S. (Intern), Hjulsager, C. K. (Intern), Skovgaard, K. (Intern), Harder, T. C. (Ekstern), Breum, S. Ø. (Intern), Larsen, L. E. (Intern)
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Scopus rating (2016): CiteScore 4.07 SJR 2.311 SNIP 1.305
Scopus rating (2015): SJR 2.365 SNIP 1.406 CiteScore 4.13
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Suppression of active, but not total MMP-3, is associated with treatment response in a phase III clinical study of rheumatoid arthritis

Objective
Biologics for rheumatoid arthritis (RA) patients with moderate to severe disease may preserve joint function. Matrix metalloproteinase 3 (MMP-3), a key tissue degrading protease, is highly elevated in RA. MMP-3, which measures the total pool of circulating MMP-3 species (cMMP3), is a commonly measured biomarker in rheumatology. The aim was to investigate the association of activated MMP-3 (actMMP3) species with treatment response compared to cMMP-3. Methods
The LITHE biomarker study (n=741) was a 1-year phase III, double-blind, placebo-controlled, parallel group study of TCZ in RA patients on stable methotrexate. cMMP-3 and actMMP-3 were assessed in fasting serum at baseline, week 4, 16, 24 and 52. Patients not achieving ACR20 remission at week 16 or 28 received rescue treatment (escapers). Spearman’s correlation was analysed between biomarker baseline level or biomarker delta and clinical measures. Changes in biomarker levels were studied as a function of time and treatment. Results
ActMMP-3 16-week change in treatment groups was predictive of 1-year radiographic progression; a small change in actMMP3 was equal to worsening radiographics. Baseline cMMP-3 was associated with 52-weeks’ radiographic status and cMMP3 16-weeks’ change was predictive of 1-year change in disease activity. ActMMP-3 was dose-dependently decreased by TCZ, and escapers decreased in actMMP-3 upon treatment. Conclusion
ActMMP-3 and cMMP-3 were found to be efficacy biomarkers of TCZ and actMMP-3 were able to differentiated doses. Moreover, the suppression of actMMP3, but not cMMP3 was associated with treatment response. This study illustrates that two biomarkers of the same protein may have different predictive capacities.
Synthetic addiction extends the productive lifetime of engineered Escherichia coli populations

Bio-production of chemicals is an important driver of the societal transition toward sustainability. However, fermentations with heavily engineered production organisms can be challenging to scale to industrial volumes. Such fermentations are subject to evolutionary pressures that select for a wide range of genetic variants that disrupt the biosynthetic capacity of the engineered organism. Synthetic product addiction that couples high-yield production of a desired metabolite to expression of nonconditionally essential genes could offer a solution to this problem by selectively favoring cells with biosynthetic capacity in the population without constraining the medium. We constructed such synthetic product addiction by controlling the expression of two nonconditionally essential genes with a mevalonic acid biosensor. The product-addicted production organism retained high-yield mevalonic acid production through 95 generations of cultivation, corresponding to the number of cell generations required for >200-m³ industrial-scale production, at which time the nonaddicted strain completely abolished production. Using deep DNA sequencing, we find that the product-addicted populations do not accumulate genetic variants that compromise biosynthetic capacity, highlighting how synthetic networks can be designed to control genetic population heterogeneity. Such synthetic redesign of evolutionary forces with endogenous processes may be a promising concept for realizing complex cellular designs required for sustainable bio-manufacturing.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Department of Biotechnology and Biomedicine
Authors: Rugbjerg, P. (Intern), Sarup-Lytzen, K. (Intern), Nagy, M. (Intern), Sommer, M. O. A. (Intern)
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The cereal pathogen *Fusarium pseudograminearum* produces a new class of active cytokinins during infection

The fungal pathogen *Fusarium pseudograminearum* causes important diseases of wheat and barley. During a survey of secondary metabolites produced by this fungus, a novel class of cytokinins, herein termed *Fusarium* cytokinins, was discovered. Cytokinins are known for their growth promoting and anti-senescence activities and the production of a cytokinin mimic by what was once considered a necrotrophic pathogen that promotes cell death and senescence challenges the simple view that this pathogen invades its hosts by employing a barrage of lytic enzymes and toxins. Through genome mining, a gene cluster in the *F. pseudograminearum* genome for the production of *Fusarium* cytokinins was identified and the biosynthetic pathway established using gene knockouts. The *Fusarium* cytokinins could activate plant cytokinin signalling, demonstrating their genuine hormone mimicry. *In planta* analysis of the transcriptional response to one *Fusarium* cytokinin suggests extensive reprogramming of the host environment by these molecules, possibly through crosstalk with defence hormone signalling pathways.
The DnaA Tale

More than 50 years have passed since the presentation of the Replicon Model which states that a positively acting initiator interacts with a specific site on a circular chromosome molecule to initiate DNA replication. Since then, the origin of chromosome replication, oriC, has been determined as a specific region that carries sequences required for binding of positively acting initiator proteins, DnaA-boxes and DnaA proteins, respectively. In this review we will give a historical overview of significant findings which have led to the very detailed knowledge we now possess about the initiation process in bacteria using Escherichia coli as the model organism, but emphasizing that virtually all bacteria have DnaA proteins that interacts with DnaA boxes to initiate chromosome replication. We will discuss the dnaA gene regulation, the special features of the dnaA gene expression, promoter strength, and translation efficiency, as well as, the DnaA protein, its concentration, its binding to DnaA-boxes, and its binding of ATP or ADP. Furthermore, we will discuss the different models for regulation of initiation which have been proposed over the years, with particular emphasis on the Initiator Titration Model.

General information
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Organisations: Department of Biotechnology and Biomedicine, Aarhus University
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Aspergillus niger secretes proteins throughout the colony except for the zone that forms asexual spores called conidia. Inactivation of flbA that encodes a regulator of G-protein signaling results in colonies that are unable to reproduce asexually and that secrete proteins throughout the mycelium. In addition, the ΔflbA strain shows cell lysis and has thinner cell walls. Expression analysis showed that 38 predicted transcription factor genes are differentially expressed in strain ΔflbA. Here, the most down-regulated predicted transcription factor gene, called fum21, was inactivated. Growth, conidiation, and protein secretion were not affected in strain Δfum21. Whole genome expression analysis revealed that 63 and 11 genes were down- and up-regulated in Δfum21, respectively, when compared to the wild-type strain. Notably, 24 genes predicted to be involved in secondary metabolism were down-regulated in Δfum21, including 10 out of 12 genes of the fumonisin cluster. This was accompanied by absence of fumonisin production in the deletion strain and a 25% reduction in production of pyranonigrin A. Together, these results link FlbA-mediated sporulation-inhibited secretion with mycotoxin production.
Asexual development, Aspergillus, Fumonisin, Fungus, Mycotoxin, Protein secretion, Secondary metabolism

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The Global Acetylome of the Human Pathogen Vibrio cholerae V52 Reveals Lysine Acetylation of Major Transcriptional Regulators

Protein lysine acetylation is recognized as an important reversible post translational modification in all domains of life. While its primary roles appear to reside in metabolic processes, lysine acetylation has also been implicated in regulating pathogenesis in bacteria. Several global lysine acetylome analyses have been carried out in various bacteria, but thus far there have been no reports of lysine acetylation taking place in the important human pathogen Vibrio cholerae. In this study, we analyzed the lysine acetylproteome of the human pathogen V. cholerae V52. By applying a combination of immuno-enrichment of acetylated peptides and high resolution mass spectrometry, we identified 3,402 acetylation sites on 1,240 proteins. Of the acetylated proteins, more than half were acetylated on two or more sites. As reported for other bacteria, we observed that many of the acetylated proteins were involved in metabolic and cellular processes and there was an over-representation of acetylated proteins involved in protein synthesis. Of interest, we demonstrated that many global transcription factors such as CRP, H-NS, IHF, Lrp and RpoN as well as transcription factors AphB, TcpP, and PhoB involved in direct regulation of virulence in V. cholerae were acetylated. In conclusion, this is the first global protein lysine acetylome analysis of V. cholerae and should constitute a valuable resource for in-depth studies of the impact of lysine acetylation in pathogenesis and other cellular processes.
The medical threat of mamba envenoming in sub-Saharan Africa revealed by genus-wide analysis of venom composition, toxicity and antivenomics profiling of available antivenoms

Mambas (genus Dendroaspis) are among the most feared of the medically important elapid snakes found in sub-Saharan Africa, but many facets of their biology, including the diversity of venom composition, remain relatively understudied. Here, we present a reconstruction of mamba phylogeny, alongside genus-wide venom gland transcriptomic and high-resolution top-down venomic analyses. Whereas the green mambas, D. viridis, D. angusticeps, D. j. jamesoni and D. j. kaimosae, express 3FTx-predominant venoms, black mamba (D. polylepis) venom is dominated by dendrotoxins I and K. The divergent terrestrial ecology of D. polylepis compared to the arboreal niche occupied by all other mambas makes it plausible that this major difference in venom composition is due to dietary variation. The pattern of intrageneric venom variability across Dendroaspis represented a valuable opportunity to investigate, in a genus-wide context, the variant toxicity of the venom, and the degree of paraspecific cross-reactivity between antivenoms and mamba venoms. To this end, the immunological profiles of the five mamba venoms were assessed against a panel of commercial antivenoms generated for the sub-Saharan Africa market. This study provides a genus-wide overview of which available antivenoms may be more efficacious in neutralising human envenomings caused by mambas, irrespective of the species responsible. The information gathered in this study lays the foundations for rationalising the notably different potency and pharmacological profiles of Dendroaspis venoms at locus resolution. This understanding will allow selection and design of toxin immunogens with a view to generating a safer and more efficacious pan-specific antivenom against any mamba envenomation.

General information
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Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal

Clear cell renal cell carcinoma (ccRCC) is characterized by near-universal loss of the short arm of chromosome 3, deleting several tumor suppressor genes. We analyzed whole genomes from 95 biopsies across 33 patients with clear cell renal cell carcinoma. We find hotspots of point mutations in the 5′ UTR of TERT, targeting a MYC-MAX-MAD1 repressor associated with telomere lengthening. The most common structural abnormality generates simultaneous 3p loss and 5q gain (36% patients), typically through chromothripsis. This event occurs in childhood or adolescence, generally as the initiating event that precedes emergence of the tumor’s most recent common ancestor by years to decades. Similar genomic changes drive inherited ccRCC. Modeling differences in age incidence between inherited and sporadic cancers suggests that the number of cells with 3p loss capable of initiating sporadic tumors is no more than a few hundred. Early development of ccRCC follows well-defined evolutionary trajectories, offering opportunity for early intervention.

Combination of whole-genome sequencing analysis and a multi-region sampling approach provides insights into the nature and timing of key oncogenic events in clear cell renal cell carcinoma, depicting the evolutionary trajectories of tumors in patients and highlights the opportunity for early intervention.

General information

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Organisations: Department of Biotechnology and Biomedicine, Center for Biological Sequence Analysis, University of Cambridge, The Francis Crick Institute, The Royal Marsden National Health Service (NHS) Foundation Trust, Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust, Wellcome Trust Sanger Institute, University of the Basque Country, University of Oxford, Hopital Europeen Georges-Pompidou, Eotvos Lorand University, University of Texas, University of St Andrews, University College London Hospitals
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Toxin-centric development approach for next-generation antivenoms

- Toxin-centric antivenom development is discussed.
- The need for geographically representative snake venoms is evaluated.
- The importance of establishing regional serpenteria is questioned.
- A design strategy for polyvalent next-generation antivenoms is presented.
Transcriptome analysis of root-knot nematode (Meloidogyne incognita)-infected tomato (Solanum lycopersicum) roots reveals complex gene expression profiles and metabolic networks of both host and nematode during susceptible and resistance responses

Root knot nematodes (RKNs, Meloidogyne incognita) are economically important endoparasites having a wide-host range. We have taken a comprehensive transcriptomic approach to investigate the expression of both tomato and RKN genes in tomato roots at five infection time intervals from susceptible plants and two infection time intervals from resistant plants, grown under soil conditions. Differentially expressed genes during susceptible (1827-tomato, 462-RKN) and resistance (25-tomato, 160-RKN) interactions were identified. In susceptible responses, tomato genes involved in cell wall structure, development, primary and secondary metabolites and defense signalling pathways along with RKN genes involved in host parasitism, development and defense are discussed. In resistance responses, tomato genes involved in secondary metabolite and hormone-mediated defense responses along with RKN genes involved in starvation stress-induced apoptosis are discussed. Also, forty novel differentially expressed RKN genes encoding secretory proteins were identified. Our findings, for the first time, provide novel insights into temporal regulation of genes involved in various biological processes from tomato and RKN simultaneously during susceptible and resistance responses, and reveals involvement of a complex network of biosynthetic pathways during disease development.

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Organisations: Department of Bio and Health Informatics, Department of Biotechnology and Biomedicine, Metagenomics, Disease Intelligence and Molecular Evolution, University of Delhi
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Scopus rating (2015): SJR 2.167 SNIP 1.633 CiteScore 4.68
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Transcriptomic profiling of interacting nasal staphylococci species reveals global changes in gene and non-coding RNA expression

Interspecies interactions between bacterial pathogens and the commensal microbiota can influence disease outcome. In the nasal cavities, Staphylococcus epidermidis has been shown to be a determining factor for Staphylococcus aureus colonization and biofilm formation. However, the interaction between S. epidermidis and S. aureus has mainly been described by phenotypic analysis, and little is known about how this interaction modulates gene expression. This study aimed to determine the interactome of nasal S. aureus and S. epidermidis isolates to understand the molecular effect of interaction. After whole-genome sequencing of two nasal staphylococcal isolates, an agar-based RNA sequencing setup was utilized to identify interaction-induced transcriptional alterations in surface-associated populations. Our results revealed differential expression of several virulence genes in both species. We also identified putative non-coding RNAs (ncRNAs) and, interestingly, detected a putative ncRNA transcribed antisense to esp, the serine protease of S. epidermidis, that has previously been shown to inhibit nasal colonization of S. aureus. In our study, the gene encoding Esp and the antisense ncRNA are both downregulated during interaction with S. aureus. Our findings contribute to a better understanding of pathogen physiology in the context of interactions with the commensal microbiota, and may provide targets for future therapeutics.
Tumstatin, a Matrikine Derived from Collagen Type IVα3, is Elevated in Serum from Patients with Non-Small Cell Lung Cancer

OBJECTIVES: Fibrosis and cancer are characterized by extracellular matrix (ECM) remodeling. The basement membrane is mainly composed by collagen type IV and laminin. Tumstatin is a matrix metalloproteinase-9 (MMP-9) generated matrikine of collagen type IV α3 chain. We evaluated the potential of tumstatin as a diagnostic biomarker of lung disorders.

METHODS: A monoclonal antibody was raised against the neo-epitope tumstatin. A novel competitive enzyme-linked immunosorbent assay for detection of tumstatin (TUM), was developed and technically characterized. Levels of TUM were measured in serum of patients with idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and non–small cell lung cancer (NSCLC) belonging to two cohorts. RESULTS: The developed TUM enzyme-linked immunosorbent assay (ELISA) was technically robust. In cohort 1, levels of TUM were significantly higher in NSCLC compared to healthy controls, IPF, and COPD (P = 0.007, P = 0.03 and P = 0.001, respectively). The area under the receiver operating characteristics (AUROC) for separation of patients with NSCLC from healthy controls was 0.97, for separation of NSCLC and IPF patients was 0.98, and for separation of NSCLC and COPD patients was 1.0. In cohort 2, levels of TUM were also significantly higher in patients with NSCLC compared to healthy controls (P = 0.002), and the AUROC for separation of NSCLC and healthy controls was 0.97. CONCLUSIONS: We developed a technically robust competitive ELISA targeting the fragment tumstatin. The level of TUM in circulation was significantly higher in patients with NSCLC compared to patients with IPF, COPD and healthy controls. The assay provided high diagnostic accuracy in separating NSCLC patients from other lung disorders and from healthy controls.
Two novel blood-based biomarker candidates measuring degradation of tau are associated with dementia: A prospective study

Truncated tau appears to be specifically related to disease pathology and recent studies have shown the presence and elevation of several truncated tau species in Cerebrospinal fluid (CSF) of subjects with Alzheimer’s disease (AD); however, the relevance of truncated Tau measurements in blood is still being studied. The aim of the current study was to assess the longitudinal associations between baseline levels of two novel blood biomarker candidates measuring truncated tau, Tau-A and Tau-C, and the risk of incident dementia and AD in elderly women. Using solid phase competitive ELISA, two tau fragments were detected in serum of 5,309 women from the Prospective Epidemiological Risk Factor study. The study was an observational, prospective study of Danish postmenopausal women. Subjects were followed with registry-linkage for up to 15 years (median follow-up time 13.7 years). Cox regression was used to assess the utility of the biomarker candidates in relation to dementia and AD. High levels of Tau-A and Tau-C (above the median) in blood were associated with lower risk of dementia and AD (Tau-A: Dementia HR[95% CI] = 0.85[0.70-1.04]; AD 0.71[0.52-0.98] and Tau-C: Dementia 0.84[0.70-1.00]; AD 0.78[0.60-1.03]). Tau-C gave a very modest increase in the AUC in a 5-year prediction horizon as compared to a reference model with age and education, while a combination of the two did not improve their predictive capacity. Measurement of tau in serum is feasible. The serological tau turnover profile may be related to the diagnosis and development of dementia and AD. The exact processing and profile in serum in relation to cognitive disorders remains to be further assessed to provide simple non-invasive tests to identify subjects with progressive cognitive disorders.

General information

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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Bio and Health Informatics, Nordic Bioscience A/S
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Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
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Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
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Using titer and titer normalized to confluence are complementary strategies for obtaining Chinese hamster ovary cell lines with high volumetric productivity of etanercept

The selection of clonally-derived Chinese hamster ovary (CHO) cell lines with the highest production rate of recombinant glycoproteins remains a big challenge during early stages of cell line development. Different strategies using either product titer or product titer normalized to cell number are being used to assess suspension-adapted clones when grown statically in microtiter plates. However, no reported study so far has performed a direct head-to-head comparison of these two early reporters for predicting clone performance. Therefore, we developed a screening platform for high-throughput analysis of titer and confluence of etanercept-producing clones. We then performed an unbiased comparison of clone ranking based on either titer or TTC-based ranking gives rise to the selection of clones with similar volumetric productivity in batch cultures. Therefore, a combinatorial titer- and TTC-based ranking is proposed, allowing for selection of distinct clones with both, high integral viable cell density (IVCD) and high specific productivity features, respectively. This contributes to selection of a versatile panel of clones that can be further characterized and from which the final producer clone can be selected that best fits the production requirements.

**General information**

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**Organisations:** Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Research Groups, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, University of Natural Resources and Life Sciences

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Bacterial cells with improved tolerance to isobutyric acid

Bacterial cells genetically modified to improve their tolerance to certain commodity chemicals, such as isobutyric acid and related compounds, and methods of preparing and using such bacterial cells for production of isobutyric acid and related compounds.

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State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Research Groups, iLoop, Bacterial Cell Factory Optimization, Global Econometric Modeling, Department of Biotechnology and Biomedicine, Bacterial Synthetic Biology, ALE Technology & Software Development
Authors: Lennen, R. (Intern), Nielsen, A. T. (Intern), Herrgård, M. (Intern), Sommer, M. O. A. (Intern), Feist, A. (Intern), Mohamed, E. T. T. (Intern)
Publication date: 16 Nov 2017
High throughput in vivo protease inhibitor selection platform

The invention relates to a recombinant microbial cell comprising a selection platform for screening for a protease inhibitor, wherein the platform comprises transgenes encoding a protease having selective peptide bond cleavage activity at a recognition site amino acid sequence; and transgenes encoding polypeptides conferring resistance to microbial growth inhibitors; wherein the polypeptides comprise the recognition site amino acid sequence cleavable by the protease. Protease inhibitors are detected by their ability to inhibit protease specific cleavage and inactivation of the polypeptides whose activity is required for conferring resistance to the microbial growth inhibitors. The invention further relates to recombinant microbial host cell libraries of metagenomic DNA that further comprise the selection platform; and the use of a recombinant microbial cell comprising the selection platform for screening for a protease inhibitor.

Bacterial cells with improved tolerance to polyols

The present invention relates to bacterial cells genetically modified to improve their tolerance to certain commodity chemicals, such as diols and other polyols, and to methods of preparing and using such bacterial cells for production of polyols and other compounds.

Bacterial cells with improved tolerance to polyols

The present invention relates to bacterial cells genetically modified to improve their tolerance to certain commodity chemicals, such as diols and other polyols, and to methods of preparing and using such bacterial cells for production of polyols and other compounds.
Bacterial cells with improved tolerance to polyamines

Provided are bacterial cells genetically modified to improve their tolerance to certain commodity chemicals, such as polyamines, and methods of preparing and using such bacterial cells for production of polyamines and other compounds.

General information
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Authors: Lennen, R. (Intern), Nielsen, A. T. (Intern), Herrgaard, M. (Intern), Sommer, M. O. A. (Intern), Feist, A. (Intern), Tharwat Tolba Mohamed, E. (Intern)
Publication date: 15 Jun 2017

A family of microbial lysine transporter polypeptides

The present invention provides a genetically modified microbial cell for production of lysine, comprising a transgene encoding a polypeptide capable of exporting lysine from the cell. The genetically modified microbial cell for production of lysine may be further characterized by genetic modifications that confer reduced lysine metabolism and/or enhanced lysine synthesis as compared to the parent cell from which said genetically modified cell was derived. The invention further provides a method for producing lysine using the genetically modified microbial cell. The invention further provides a novel family of lysine transporter polypeptides; and the use of said polypeptide to enhance production of extracellular lysine in a microbial cell.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, iLoop, Department of Biotechnology and Biomedicine, Bacterial Synthetic Biology
Authors: Malla, S. (Intern), Sommer, M. O. A. (Intern), van der Helm, E. (Intern), Wieschalka, S. (Ekstern), Förster, J. (Intern)
Publication date: 26 May 2017
Localization and in-vivo characterization of *Thapsia garganica* CYP76AE2 indicates a role in thapsigargin biosynthesis

The Mediterranean plant *Thapsia garganica* (dicot, Apiaceae), also known as deadly carrot, produces the highly toxic compound thapsigargin. This compound is a potent inhibitor of the sarcoplasmic-endoplasmic reticulum Ca\(^{2+}\) -ATPase calcium pump in mammals and is of industrial importance as the active moiety of the anticancer drug mipsagargin, currently in clinical trials. Knowledge of thapsigargin in planta storage and biosynthesis has been limited. Here, we present the putative second step in thapsigargin biosynthesis, by showing that the cytochrome P450 TgCYP76AE2, transiently expressed in *Nicotiana benthamiana*, converts epikunzeaol into epidihydrocostunolide. Furthermore, we show that thapsigargin is likely to be stored in secretory ducts in the roots. Transcripts from TgTPS2 (epikunzeaol synthase) and TgCYP76AE2 in roots were found only in the epithelial cells lining these secretory ducts. This emphasizes the involvement of these cells in the biosynthesis of thapsigargin. This study paves the way for further studies of thapsigargin biosynthesis.
Random sequences are an abundant source of bioactive RNAs or peptides

It is generally assumed that new genes arise through duplication and/or recombination of existing genes. The probability that a new functional gene could arise out of random non-coding DNA is so far considered to be negligible, as it seems unlikely that such an RNA or protein sequence could have an initial function that influences the fitness of an organism. Here, we have tested this question systematically, by expressing clones with random sequences in Escherichia coli and subjecting them to competitive growth. Contrary to expectations, we find that random sequences with bioactivity are not rare. In our experiments we find that up to 25% of the evaluated clones enhance the growth rate of their cells and up to 52% inhibit growth. Testing of individual clones in competition assays confirms their activity and provides an indication that their activity could be exerted by either the transcribed RNA or the translated peptide. This suggests that transcribed and translated random parts of the genome could indeed have a high potential to become functional. The results also suggest that random sequences may become an effective new source of molecules for studying cellular functions, as well as for pharmacological activity screening.
Chronic lymphocytic leukemia (CLL) is the most common adult leukemia with still unclear etiology. Indications of antigenic pressure have been hinted, using sequence and structure-based reasoning. The accuracy of such approaches, and in particular of the ones derived from 3D models obtained from the patients’ antibody amino acid sequences, is intimately connected to both the reliability of the models and the quality of the methods used to compare and group them. The proposed work provides a sophisticated method for the classification of CLL patients based on clustering the amino acid sequences of the clonotypic B-cell receptor immunoglobulin, which is the ideal clone-specific marker, critical for clonal behavior and patient outcome. A novel CLL patient clustering method is hereby proposed, combining bioinformatics methods with the extraction of 3D object descriptors, used in machine learning applications. The proposed methodology achieved an efficient and highly informative grouping of CLL patients in accordance to their biological and clinical properties.
Activation of Toll-like Receptor 2 in Human Synovium Explants Increase Tissue Turnover and Secretion of Interleukin-6

Background/Purpose:
The innate immune system is important for initiation and development of OA. Increased degradation of the cartilage release fragments into the synovial fluid, which can then bind to innate immune receptors in the synovium. The aim of this study was to investigate the effect of Toll like receptor 2 (TLR2) activation by synthetic agonists and a synthetic aggrecan 32 amino acid fragment (32-mer) on the tissue turnover and IL-6 secretion, in a human synovial membrane explant model.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, University of Copenhagen, Gentofte University Hospital, Nordic Bioscience A/S
Authors: Sharma, N. (Ekstern), Kayed, A. (Ekstern), Kjelgaard-Petersen, C. F. (Intern), Christiansen, T. G. (Ekstern), Karsdal, M. (Ekstern), Thudium, C. S. (Ekstern), Bay-Jensen, A. (Ekstern)
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A Dereplication and Bioguided Discovery Approach to Reveal New Compounds from a Marine-Derived Fungus Stilbella fimetaria

A marine-derived *Stilbella fimetaria* fungal strain was screened for new bioactive compounds based on two different approaches: (i) bio-guided approach using cytotoxicity and antimicrobial bioassays; and (ii) dereplication based approach using liquid chromatography with both diode array detection and high resolution mass spectrometry. This led to the discovery of several bioactive compound families with different biosynthetic origins, including pimarane-type diterpenoids and hybrid polyketide-non ribosomal peptide derived compounds. Prefractionation before bioassay screening proved to be a great aid in the dereplication process, since separate fractions displaying different bioactivities allowed a quick tentative identification of known antimicrobial compounds and of potential new analogues. A new pimarane-type diterpene, myrocin F, was discovered in trace amounts and displayed cytotoxicity towards various cancer cell lines. Further media optimization led to increased production followed by the purification and bioactivity screening of several new and known pimarane-type diterpenoids. A known broad-spectrum antifungal compound, ilicicolin H, was purified along with two new analogues, hydroxyl-ilicicolin H and ilicicolin I, and their antifungal activity was evaluated.

**General information**

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Advanced fabrication of porous ceramic multilayers for membrane applications

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Organisations: Department of Energy Conversion and Storage, Ceramic Engineering & Science, Proton conductors, Department of Biotechnology and Biomedicine, Department of Chemical and Biochemical Engineering
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Affinity Electrophoresis for Analysis of Catalytic Module-Carbohydrate Interactions
Affinity electrophoresis has long been used to study the interaction between proteins and large soluble ligands. The technique has been found to have great utility for the examination of polysaccharide binding by proteins, particularly carbohydrate binding modules (CBMs). In recent years, carbohydrate surface binding sites of proteins mostly enzymes have also been investigated by this method. Here, we describe a protocol for identifying binding interactions between
A highly active endo-levanase BT1760 of a dominant mammalian gut commensal Bacteroides thetaiotaomicron cleaves not only various bacterial levan, but also levan of timothy grass

Bacteroides thetaiotaomicron, an abundant commensal of the human gut, degrades numerous complex carbohydrates. Recently, it was reported to grow on a β-2,6-linked polyfructan levan produced by Zymomonas mobilis degrading the polymer into fructooligosaccharides (FOS) with a cell surface bound endo-levanase BT1760. The FOS are consumed by B. thetaiotaomicron, but also by other gut bacteria, including health-promoting bifidobacteria and lactobacilli. Here we characterize biochemical properties of BT1760, including the activity of BT1760 on six bacterial levan synthesized by the levensucrase Lsc3 of Pseudomonas syringae pv. tomato, its mutant Lsc3Asp300Asn, levensucrases of Zymomonas mobilis, Erwinia herbicola, Halomonas smyrnensis as well as on levan isolated from timothy grass. For the first time a plant levan is shown as a perfect substrate for an endo-fructanase of a human gut bacterium. BT1760 degraded levan to FOS with degree of polymerization from 2 to 13. At optimal reaction conditions up to 1 g of FOS were produced per 1 mg of BT1760 protein. Low molecular weight (<60 kDa) levan, including timothy grass levan and levan synthesized from sucrose by the Lsc3Asp300Asn, were degraded most rapidly whilst levan produced by Lsc3 from raffinose least rapidly. BT1760 catalyzed finely at human body temperature (37°C) and in moderately acidic environment (pH 5-6) that is typical for the gut lumen. According to differential scanning fluorimetry, the Tm of the endo-levanase was 51.5°C. All tested levan were sufficiently stable in acidic conditions (pH 2.0) simulating the gastric environment. Therefore, levan of both bacterial and plant origin may serve as a pre-biotic fiber for B. thetaiotaomicron and contribute to short-chain fatty acids synthesis by gut microbiota. In the genome of Bacteroidesxylanisolvens of human origin a putative levan degradation locus was disclosed.
Allergic Sensitization at School Age is a Systemic Low-grade Inflammatory Disorder

Background
Systemic low-grade inflammation has been demonstrated in a range of the frequent noncommunicable diseases (NCDs) proposing a shared mechanism, but is largely unexplored in relation to allergic sensitization. We therefore aimed to investigate the possible association with childhood allergic sensitization.

Methods
High-sensitivity C-reactive protein (hs-CRP), interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and chemokine (C-X-C motif) ligand 8 (CXCL8) were measured in plasma at age 6 months (N = 214) and 7 years (N = 277) in children from the Copenhagen Prospective Studies on Asthma in Childhood2000 (COPSAC2000) birth cohort. Allergic sensitization against common inhalant and food allergens was determined longitudinally at ages ½, 1½, 4 and 6 years by
specific IgE assessments and skin prick tests. Associations between inflammatory biomarkers and sensitization phenotypes were tested with logistic regression and principal component analyses (PCAs).

Results
Adjusted for gender, recent infections, and a CRP genetic risk score, hs-CRP at 7 years was associated with concurrent elevated specific IgE against any allergen [adjusted OR (aOR) = 1.40; 95% CI, 1.14–1.72; \( P = 0.001 \)], aeroallergens (aOR, 1.43; 1.15–1.77; \( P = 0.001 \)), food allergens (aOR, 1.31; 95% CI, 1.02–1.67; \( P = 0.04 \)), sensitization without any clinical allergy symptoms (aOR = 1.40; 1.06–1.85; \( P = 0.02 \)), and with similar findings for skin prick tests. The other inflammatory markers were not univariately associated with sensitization, but multiparametric PCA suggested a specific inflammatory response among sensitized children. Inflammatory markers at age 6 months were not associated with subsequent development of sensitization phenotypes.

Conclusions
Elevated hs-CRP is associated with allergic sensitization in school-aged children suggesting systemic low-grade inflammation as a phenotypic characteristic of this early-onset NCD.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, University of Copenhagen
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A meta-proteomics approach to study the interspecies interactions affecting microbial biofilm development in a model community

Microbial biofilms are omnipresent in nature and relevant to a broad spectrum of industries ranging from bioremediation and food production to biomedical applications. To date little is understood about how multi-species biofilm communities develop and function on a molecular level, due to the complexity of these biological systems. Here we apply a meta-proteomics approach to investigate the mechanisms influencing biofilm formation in a model consortium of four bacterial soil isolates; Stenotrophomonas rhizophila, Xanthomonas retroflexus, Microbacterium oxydans and Paenibacillus amylolyticus. Protein abundances in community and single species biofilms were compared to describe occurring interspecies interactions and the resulting changes in active metabolic pathways. To obtain full taxonomic resolution between closely related species and empower correct protein quantification, we developed a novel pipeline for generating reduced reference proteomes for spectral database searches. Meta-proteomics profiling indicated that community development is dependent on cooperative interactions between community members facilitating cross-feeding on specific amino acids. Opposite regulation patterns of fermentation and nitrogen pathways in Paenibacillus amylolyticus and Xanthomonas retroflexus may, however, indicate that competition for limited resources also affects community development. Overall our results demonstrate the multitude of pathways involved in biofilm formation in mixed communities.

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Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, National Veterinary Institute, T-cells & Cancer, University of Copenhagen
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A modular metabolic engineering approach for the production of 1,2-propanediol from glycerol by *Saccharomyces cerevisiae*

Compared to sugars, a major advantage of using glycerol as a feedstock for industrial bioprocesses is the fact that this molecule is more reduced than sugars. A compound whose biotechnological production might greatly profit from the substrate's higher reducing power is 1,2-propanediol (1,2-PDO). Here we present a novel metabolic engineering approach to produce 1,2-PDO from glycerol in *S. cerevisiae*. Apart from implementing the heterologous methylglyoxal (MG) pathway for 1,2-PDO formation from dihydroxyacetone phosphate (DHAP) and expressing a heterologous glycerol facilitator, the employed genetic modifications included the replacement of the native FAD-dependent glycerol catabolic pathway by the ‘DHA pathway’ for delivery of cytosolic NADH and the reduction of triosephosphate isomerase (TPI) activity for increased precursor (DHAP) supply. The choice of the medium had a crucial impact on both the strength of the metabolic switch towards fermentation in general (as indicated by the production of ethanol and 1,2-PDO) and on the ratio at which these two fermentation products were formed. For example, virtually no 1,2-PDO but only ethanol was formed in synthetic glycerol medium with urea as the nitrogen source. When nutrient-limited complex YG medium was used, significant amounts of 1,2-PDO were formed and it became obvious that the concerted supply of NADH and DHAP are essential for boosting 1,2-PDO production. Additionally, optimizing the flux into the MG pathway improved 1,2-PDO formation at the expense of ethanol. Cultivation of the best-performing strain in YG medium and a controlled bioreactor set-up resulted in a maximum titer of > 4gL-1 1,2-PDO which, to the best of our knowledge, has been the highest titer of 1,2-PDO obtained in yeast so far. Surprisingly, significant 1,2-PDO production was also obtained in synthetic glycerol medium after changing the nitrogen source towards ammonium sulfate and adding a buffer.
An extracellular cell-attached pullulanase confers branched α-glucan utilization in human gut Lactobacillus acidophilus

Of the few predicted extracellular glycan-active enzymes, glycoside hydrolase family 13 subfamily 14 (GH13_14) pullulanases are the most common in human gut lactobacilli. These enzymes share a unique modular organization, not observed in other bacteria, featuring a catalytic module, two starch binding modules, a domain of unknown function, and a C-terminal surface layer association protein (SLAP) domain. Here we explore the specificity of a representative of this group of pullulanases, LaPul13_14 and its role in branched α-glucans metabolism in the well characterized Lactobacillus acidophilus NCFM that is widely used as a probiotic. Growth experiments of L. acidophilus NCFM on starch-derived branched substrates revealed preference for α-glucans with short branches of about two to three glucosyl moieties over amylopectin with longer branches. Cell-attached debranching activity was measurable in the presence of α-glucans but was repressed by glucose. The debranching activity is conferred exclusively by LaPul13_14 and is abolished in a mutant strain lacking a functional LaPul13_14 gene. Hydrolysis kinetics of recombinant LaPul13_14 confirmed the preference for short branched α-glucan oligomers consistent with the growth data. Curiously, this enzyme displayed the highest catalytic efficiency and the lowest Km reported for a pullulanase. Inhibition kinetics revealed mixed inhibition by β-cyclodextrin suggesting the presence of additional glucan binding sites besides the active site of the enzyme, which may contribute to the unprecedented substrate affinity. The enzyme also displays high thermostability and higher activity in the acidic pH range reflecting adaptation to the physiologically challenging conditions in the human gut.IMPORTANCE Starch is one of the most abundant glycans in human diet. Branched α-1,6-glucans in dietary starch and glycogen are non-degradable by human enzymes and constitute a metabolic resource for the gut microbiota. The role of health-beneficial lactobacilli prevalent in the human small intestine in starch metabolism remains unexplored in contrast to colonic bacterial residents. This study highlights the pivotal role of debranching enzymes in the break-down of starchy branched α-glucan oligomers (α-limit dextrins) by human gut lactobacilli exemplified by Lactobacillus acidophilus NCFM, which is one of the best characterized strains used as probiotics. Our data bring novel insight into the metabolic preference of L. acidophilus for α-glucans with short α-1,6-branches. The unprecedented affinity of the debranching enzyme that confers growth on these substrates reflects its adaptation to the nutrient-competitive gut ecological niche and constitutes a potential advantage in cross-feeding from human and bacterial dietary starch metabolism.
A novel biomarker of laminin turnover is associated with mortality and disease progression in chronic kidney disease

INTRODUCTION AND AIMS: Patients with chronic kidney disease (CKD) have increased risk of progressing to end-stage renal disease (ESRD) and a high mortality rate. One of the major underlying causes of progression of renal failure is renal fibrosis, which is caused by dysregulated extracellular matrix (ECM) remodeling. The laminin γ1 (LAMC1) chain is a constituent of the laminin types present in the glomerular basement membrane (GBM), and its turnover may be altered in CKD. Fragments of LAMC1 could quantify GBM turnover in human CKD and reflect pathological tissue changes. We developed an immunoassay targeting LG1M, a neo-epitope of LAMC1 generated by matrix metalloproteinases (MMPs). We then measured LG1M levels in serum and urine from a large prospective cohort of patients with high-risk CKD.

General information
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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Nordic Bioscience A/S, Queen Elizabeth Hospital Birmingham, University of Southern Denmark
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Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.105 SNIP 1.207
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Scopus rating (2005): SJR 1.039 SNIP 1.12
Scopus rating (2004): SJR 0.803 SNIP 1.013
A novel Dual Amylin and Calcitonin Receptor Agonist (DACRA), KBP-089, induces weight loss through a reduction in fat, but not lean mass, while improving food preference

Background and Purpose
Obesity and associated co-morbidities, such as type 2 diabetes and non-alcoholic fatty liver disease, are major health challenges – hence, development of weight loss therapies with the ability to reduce the co-morbidities is key.

Experimental Approach
The effect of the dual amylin and calcitonin receptor agonist (DACRA), KBP-089, on bodyweight, glucose homeostasis, and fatty acid accumulation in liver and muscle tissue, food preference was investigated. Further, we elucidate weight-independent effects of KBP-089 using a weight-matched group.

Key Results
High fat diet fed rats were treated with KBP-089 s.c., at 0.625, 1.25, 2.5 µg·kg⁻¹ and vehicle resulting in a dose-dependent and sustained ~17% weight loss by the 2.5 µg·kg⁻¹ (p < 0.001). Moreover, KBP-089 reduced fat depot size and reduced lipid accumulation in muscle and liver.
In Zucker Diabetic Fatty rats, KBP-089 improved glucose homeostasis through improved insulin action. To obtain a weight-matched group, significantly less food was offered (9% less than in the KBP-089 group). Weight-matching led to improved glucose homeostasis through lowered plasma insulin; however, these were inferior to the effect of KBP-089.
In the food preference test, normal diet rats obtained 74% of their calories from chocolate. KBP-089 administration reduced total caloric intake, and induced a relative increase in chow consumption while drastically lowering the chocolate compared to vehicle.

Conclusion
The novel DACRA, KBP-089 induces a sustained weight loss, leading to improved metabolic parameters including food preference, and these are beyond those observed simply by diet-induced weight loss.
A novel urinary biomarker of type VI collagen formation and endotrophin is associated with loss of kidney function in patients with diabetic nephropathy

INTRODUCTION AND AIMS: Diabetic nephropathy (DN) is the leading cause of CKD in the Western world. Around 50 percent of patients who have had diabetes for more than 20 years develop CKD. Glomerulosclerosis and tubulointerstitial fibrosis are histological features as DN progresses towards end-stage renal disease. Fibrosis is characterized by a dysregulated remodeling of the extracellular matrix (ECM). Collagen type VI (COL VI) is a crucial ECM molecule for the control of tissue organization. It is present at the interface of the glomerular basement membrane and interstitial matrix and its levels have been reported elevated in glomeruli of patients with glomerular diseases and in the mesangium of diabetic patients. During deposition of COL VI, a fragment is released, namely endotrophin (ETP). Endotrophin (ETP), has shown pro-fibrotic potential. We investigated the prognostic potential of COL VI formation and ETP for CKD prog
A novel urinary biomarker of type VI collagen formation and endotrophin is associated with loss of kidney function in patients with diabetic nephropathy.pdf

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**Anthelmintic effects of forage chicory (Cichorium intybus) against free-living and parasitic stages of Cooperia oncophora**

Chicory shows great promise as an anthelmintic forage for grazing ruminants that can reduce reliance on anti-parasitic drugs. Recently, we reported potent anthelmintic effects of chicory-based diets in infected cattle with significant reductions in worm burdens of the abomasal nematode Ostertagia ostertagi, whilst no apparent activity was observed against the small intestinal parasite Cooperia oncophora. To explore this discrepancy, we investigated direct anthelmintic effects of forage chicory against *C. oncophora* in vitro. Chicory leaves (cultivar ‘Spadona’) were extracted with methanol in a Soxhlet apparatus and the resulting extract was purified by solid-phase extraction to concentrate bioactive phytochemicals such as sesquiterpene lactones. *C. oncophora* eggs and adult worms from mono-infected donor calves were exposed to decreasing concentrations of the chicory extract. In an egg hatch assay, the chicory extract induced a marked and dose-dependent inhibition of egg hatching, with 95% inhibition at 2500 μg extract/mL (EC50 = 619 [95% CI: 530–722] μg extract/mL). In the adult motility inhibition assays, the chicory extract induced a potent and dose-dependent worm paralysis. At 12 h of incubation, worms exposed to chicory showed a total paralysis at ≥500 μg extract/mL, while after 48 h of incubation a complete inhibition of worm motility was observed at ≥250 μg extract/mL (EC50 = 80 [95% CI: 67–95] μg extract/mL). We have demonstrated that forage chicory can induce potent inhibitory effects on the egg hatching and exert direct anthelmintic activity against parasitic stages of *C. oncophora*. These results suggest that the previously reported absence of in vivo effects of chicory towards *C. oncophora* in infected animals may be related with host-mediated factors and/or inhibitory digestive conditions, rather than an inherent inactivity of chicory and its bioactive phytochemicals.

**General information**

**State:** Published

**Organisations:** National Veterinary Institute, Department of Biotechnology and Biomedicine, Photosynthetic Cell Factories, University of Copenhagen, Norwegian Veterinary Institute

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- **Scopus rating (2011):** SJR 1.233 SNIP 1.429 CiteScore 2.61
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Complex interactions between pathogenic bacteria, the microbiota, and the host can modify pathogen physiology and behavior. We describe two different experimental approaches to study microbe-microbe interactions in in vitro systems containing surface-associated microbial populations. One method is the application of RNA sequencing (RNA-seq) to determine the transcriptional changes in pathogenic bacteria in response to microbial interspecies interactions. The other method combines flow cell devices for bacterial cultivation and growth with high-resolution bioimaging to analyze the microscale structural organization of interacting microbial populations within mixed-species biofilms.

**Application of RNA-seq and Bioimaging Methods to Study Microbe-Microbe Interactions and Their Effects on Biofilm Formation and Gene Expression**

Complex interactions between pathogenic bacteria, the microbiota, and the host can modify pathogen physiology and behavior. We describe two different experimental approaches to study microbe-microbe interactions in in vitro systems containing surface-associated microbial populations. One method is the application of RNA sequencing (RNA-seq) to determine the transcriptional changes in pathogenic bacteria in response to microbial interspecies interactions. The other method combines flow cell devices for bacterial cultivation and growth with high-resolution bioimaging to analyze the microscale structural organization of interacting microbial populations within mixed-species biofilms.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, Infection Microbiology
Authors: Amador Hierro, C. I. (Intern), Stemberg, C. (Intern), Jelsbak, L. (Intern)
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Application of the thermostable β-galactosidase, BgaB, from Geobacillus stearothermophilus as a versatile reporter under anaerobic and aerobic conditions

Use of thermophilic organisms has a range of advantages, but the significant lack of engineering tools limits their applications. Here we show that β-galactosidase from Geobacillus stearothermophilus (BgaB) can be applicable in a range of conditions, including different temperatures and oxygen concentrations. This protein functions both as a marker, promoting colony color development in the presence of a lactose analogue S-gal, and as a reporter enabling quantitative measurement by a simple colorimetric assay. Optimal performance was observed at 70 °C and pH 6.4. The gene was introduced into G. thermoglucosidans. The combination of BgaB expressed from promoters of varying strength with S-gal produced distinct black colonies in aerobic and anaerobic conditions at temperatures ranging from 37 to 60 °C. It showed an important advantage over the conventional β-galactosidase (LacZ) and substrate X-gal, which were inactive at high temperature and under anaerobic conditions. To demonstrate the versatility of the reporter, a promoter library was constructed by randomizing sequences around −35 and −10 regions in a wild type groES promoter from Geobacillus sp. GHH01. The library contained 28 promoter variants and encompassed fivefold variation. The experimental pipeline allowed construction and measurement of expression levels of the library in just 4 days. This β-galactosidase provides a promising tool for engineering of aerobic, anaerobic, and thermophilic production organisms such as Geobacillus species.
A Review of Biotechnological Artemisinin Production in Plants

Malaria is still an eminent threat to major parts of the world population mainly in sub-Saharan Africa. Researchers around the world continuously seek novel solutions to either eliminate or treat the disease. Artemisinin, isolated from the Chinese medicinal herb Artemisia annua, is the active ingredient in artemisinin-based combination therapies used to treat the disease. However, naturally artemisinin is produced in small quantities, which leads to a shortage of global supply. Due to its complex structure, it is difficult chemically synthesize. Thus to date, A. annua remains as the main commercial source of artemisinin. Current advances in genetic and metabolic engineering drives to more diverse approaches and developments on improving in planta production of artemisinin, both in A. annua and in other plants. In this review, we describe efforts in bioengineering to obtain a higher production of artemisinin in A. annua and stable heterologous in planta systems. The current progress and advancements provides hope for significantly improved production in plants.
A safflower oil-based high fat/high-sucrose diet modulates the gut microbiota and liver phospholipid profiles associated with early glucose intolerance in the absence of tissue inflammation

n-6 PUFA-rich diets are generally considered obesogenic in rodents. Here we examined how long-term intake of a high fat/high sucrose (HF/HS) diet based on safflower oil affected metabolism, inflammation and gut microbiota composition. We fed male C57BL/6J mice a HF/HS diet based on safflower oil - rich in n-6 PUFAs - or low-fat/low-sucrose (LF/LS) diet for 40 weeks. Compared to the LF/LS diet, intake of the safflower-based HF/HS diet only led to moderate weight gain, while glucose intolerance developed at week 5 prior to signs of inflammation, but concurrent with increased levels of linoleic acid and arachidonic acid in hepatic phospholipids. Intake of the HF/HS diet resulted in early changes in the gut microbiota, including an increased abundance of Blautia, while late changes coincided with altered inflammatory profiles and increased fasting plasma insulin. Analysis of immune cells in visceral fat and liver revealed no differences between diets before week 40, where the number of immune cells decreased in the liver of HF/HS-fed mice. We suggest that a diet-dependent increase in the n-6 to n-3 PUFA ratio in hepatic phospholipids together with gut microbiota changes contributed to early development of glucose intolerance without signs of inflammation. This article is protected by copyright. All rights reserved.
A serum biomarker reflecting collagen type I degradation (C1M) is an independent risk factor for acute myocardial infarction in postmenopausal women: results from the PERF study

Cardiovascular disease (CVD) is the leading cause of death in postmenopausal women, and symptoms of ischemic heart disease (IHD) and acute myocardial infarction (AMI) are often overlooked. With the loss of estrogen production collagen stability is affected with potential of an increased risk of unstable plaques in coronary vessels. Collagen type I, a major component of the cardiac extracellular matrix (ECM), is cleaved by matrix metalloproteinases (MMPs) and known to be active remodeled in CVD.
Aspergilli: Models for systems biology in filamentous fungi
Aspergillus is a diverse genus of filamentous fungi including common household mold as well as human pathogens. More than 350 species are currently part of this genus and all their genomes are soon to be sequenced. The availability of this vast amount of data will allow for more in-depth understanding of genetic traits governing desirable properties like enzyme production as well as the pathogenic potency of the organisms. In this review we give an overview of the systems biology research conducted in Aspergilli. This research has covered omics technologies like genomics, transcriptomics and proteomics where outstanding contributions are highlighted. From past developments it becomes apparent that CRISPR technology will speed up genetic research in the Aspergillus field. This speed up will allow for an increase in systems biology targeted research by accelerating data generation. The increase in throughput of data generation both per experiment and per time will lead to future challenges in the data handling, integration and interpretation.

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State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Brandl, J. (Intern), Andersen, M. R. (Intern)
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Association among bile acids, the human gut microbiome and metabolic diseases

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Organisations: Department of Bio and Health Informatics, Metagenomics, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Clinical-Microbiomics ApS
Authors: Petersen, A. Ø. (Intern), Myers, P. N. (Intern), Nielsen, H. B. (Ekstern)
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A study of associations between early DHA status and fatty acid desaturase (FADS) SNP and developmental outcomes in children of obese mothers

DHA from diet or endogenous synthesis has been proposed to affect infant development, however, results are inconclusive. In this study, we aim to verify previously observed fatty acid desaturase gene cluster (FADS) SNP-specific associations with erythrocyte DHA status in 9-month-old children and sex-specific association with developmental outcomes. The study was performed in 166 children (55 % boys) of obese mothers. Erythrocyte fatty acid composition was analysed in blood-samples obtained at 9 months of age, and developmental outcomes assessed by the Ages and Stages Questionnaire at 3 years. Erythrocyte DHA level ranged from 4·4 to 9·9 % of fatty acids, but did not show any association with FADS SNP or other potential determinants. Regression analysis showed associations between erythrocyte DHA and scores for personal-social skills (β 1·8 (95 % CI 0·3, 3·3), P=0·019) and problem solving (β 3·4 (95 % CI 1·2, 5·6), P=0·003). A tendency was observed for an association in opposite direction between minor alleles (G-variant) of rs1535 and rs174575 and personal-social skills (P=0·062 and 0·068, respectively), which became significant when the SNP were combined based on their previously observed effect on erythrocyte DHA at 9 months of age (β 2·6 (95 % CI 0·01, 5·1), P=0·011). Sex-SNP interaction was indicated for rs174575 genotype on fine motor scores (P=0·016), due to higher scores among minor allele carrying girls (P=0·043), whereas no effect was seen among boys. In conclusion, DHA-increasing FADS SNP and erythrocyte DHA status were consistently associated with improved personal-social skills in this small cohort of children of obese mothers irrespective of sex, but the sample was too small to verify potential sex-specific effects.

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Organisations: Department of Biotechnology and Biomedicine, Systems Metabolic Lipidology, University of Copenhagen, Rigshospitalet
Authors: Andersen, K. R. (Ekstern), Harsløf, L. B. S. (Ekstern), Schnurr, T. M. (Ekstern), Hansen, T. (Ekstern), Hellgren, L. (Intern), Michaelsen, K. F. (Ekstern), Lauritzen, L. (Ekstern)
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Web of Science (2016): Indexed yes
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.532 SNIP 1.273 CiteScore 3.18
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Scopus rating (2013): SJR 2.746 SNIP 2.479 CiteScore 3.61
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Scopus rating (2010): SJR 1.236 SNIP 1.253
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.627 SNIP 0.572
Web of Science (2009): Indexed yes
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Scopus rating (2008): SJR 0.966 SNIP 1.2
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Scopus rating (2007): SJR 0.987 SNIP 1.255
Web of Science (2007): Indexed yes
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Web of Science (2006): Indexed yes
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Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 0.626 SNIP 1.088
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Web of Science (2003): Indexed yes
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Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.838 SNIP 1.515
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 0.609 SNIP 1.611
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 0.568 SNIP 1.156
A survey of xerophilic Aspergillus from indoor environment, including descriptions of two new section Aspergillus species producing eueotium-like sexual states

Xerophilic fungi grow at low water activity or low equilibrium relative humidity and are an important part of the indoor fungal community, of which Aspergillus is one of the dominant genera. A survey of xerophilic fungi isolated from Canadian and Hawaiian house dust resulted in the isolation of 1039 strains; 296 strains belong to Aspergillus and represented 37 species. Reference sequences were generated for all species and deposited in GenBank. Aspergillus sect. Aspergillus (formerly called Eurotium) was one of the most predominant groups from house dust with nine species identified. Additional cultures deposited as Eurotium were received from the Canadian Collection of Fungal Cultures and were also re-identified during this study. Among all strains, two species were found to be new and are introduced here as A. mallochii and A. megasporus. Phylogenetic comparisons with other species of section Aspergillus were made using sequences of ITS, beta-tubulin, calmodulin and RNA polymerase II second largest subunit. Morphological observations were made from cultures grown under standardized conditions. Aspergillus mallochii does not grow at 37 degrees C and produces roughened ascospores with incomplete equatorial furrows. Aspergillus megasporus produces large conidia (up to 12 μm diam) and roughened ascospores with equatorial furrows. Echinulin, quinolactacin A(1) & A(2), preechinulin and neoechinulin A & B were detected as major extrolites of A. megasporus, while neoechinulin A & B and isoechinulin A, B & C were the major extrolites from A. mallochii.

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Bacterial gangs: United and strong by means of quorum sensing

Microorganisms can effectively communicate with each other. They share information about their community size (quorum), and thereby their nutrient requirement, then take appropriate action such as moving away. They use signalling molecules to coordinate their behaviour. These compounds, like similar molecules in humans, are called pheromones.

General information
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Authors: Kuipers, O. P. (Ekstern), Kovács, Á. T. (Intern)
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Bacterial resistance and susceptibility to antimicrobial peptides and peptidomimetics
Bacterial resistance to conventional antibiotics has become a global challenge and there is an urgent need for new and alternative compounds. Antimicrobial peptides (AMPs) are under investigation as novel antibiotics. These are part of the immunodefense of all living organisms; hence, they represent a valid candidate both for their antibacterial activity and for their immunomodulation features. However, these compounds have several disadvantages once administered in vivo. These shortcomings have led to extensive attempts of improving their features with rational synthesis and design. Peptidomimetics are one class of such synthetic modified peptides. The purpose of this PhD project was to determine the antibacterial spectrum and potential use of synthetic antimicrobial peptides and peptidomimetics. Another key investigation has been the experimental development of resistance to these novel antibacterial agents. We investigated (Article 1) the antibacterial effect of selected peptidomimetics in a simulated in vivo environment using human blood plasma and serum. We speculated that the activity of peptidomimetics was hampered by the presence of blood fluids. However, the antibacterial activity was enhanced in presence of human blood plasma but not in presence of human blood serum. We hypothesized that the complex system of clotting factors present in plasma but not in serum were causing the enhanced effect of peptidomimetics. Interestingly, the resistance to the activated blood matrices of the activity of the compounds decreased dramatically when exposed to human plasma, but not to human serum. We hypothesized that complement system and other factors present in human plasma interact synergistically with membrane active compounds such as AMPs, and that the concentrations of peptidomimetics and peptide antibiotics needed in vivo may be lower than predicted from standard antimicrobials susceptibility testing.

Unfortunately, bacterial resistance to AMPs can be adapted by in laboratory settings, and we found (Manuscript 2) that in Escherichia coli through a daptive evolution experiment. We hypothesized that evolution of resistance to the combination would be slower than to the single compounds. However, the lineages exposed to P9-4 (alone or in combination) were the slowest adapting compared to the other treatments. We suggest that the AMP P9-4 could be considered a promising candidate for future application in clinical settings. Because of the low resistance development rate.

Using whole-genome sequencing, we investigated the genetic basis of resistance in the adapted lineages and derived clones. Deletions in the gene encoding for the enzyme CDP-glycerophosphotransferase were the most common variants, indicating that a common consequence of mutation events had led to an increase in the number of resistance. The deletion of the enzyme reduced the susceptibility to the antibiotic. Several clones retained resistance after cultivation in absence of compound. Genome analyses demonstrated that deletions in the gene encoding for the enzyme CDP-glycerophosphotransferase were still present after cultivation. Thus, this enzyme may be a key role in the mechanism of resistance. Cross-resistance is a common feature of resistant microorganisms and therefore determined whether the adapted resistant clones had altered susceptibility to other antibiotics. Several resistant clones were resistant to compounds with intracellular activity. However, the same clones were susceptible to the wild type when exposed to membrane-active compounds with specific features such as lipophilicity, incorporation of D-amino acids, and presence of R-motifs. Thus, the concern that AMP-resistant clones may be a threat to our immunity may be overestimated.
In conclusion, this PhD project supports the belief that bacteria hold the potential to develop resistance to each novel antibacterial agent. Nevertheless, strategies to circumvent resistance exist and must be pursued.

**Bioactive Lipids in Dairy Fat**
Milk fat is the most important energy source for the newborn infant beside its important role as energy source, milk fat also contain a range of bioactive lipids, that potentially can modulate the immune response and metabolic regulation in the child. In this chapter we review the literature on bioactive dairy fatty acids: conjugated linoleic acid, branched chained and odd chained fatty acids, as well as bioactive complex lipids such as sphingomyelin and gangliosides.

**Biosynthesis of acurin A and B in Aspergillus aculeatus**

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Biosynthesis of the antimicrobial cyclic lipopeptides nunamycin and nunapeptin by Pseudomonas fluorescens strain In5 is regulated by the LuxR-type transcriptional regulator NunF

Nunamycin and nunapeptin are two antimicrobial cyclic lipopeptides (CLPs) produced by Pseudomonas fluorescens In5 and synthesized by nonribosomal synthetases (NRPS) located on two gene clusters designated the nun-nup regulon. Organization of the regulon is similar to clusters found in other CLP-producing pseudomonads except for the border regions where putative LuxR-type regulators are located. This study focuses on understanding the regulatory role of the LuxR-type-encoding gene nunF in CLP production of P. fluorescens In5. Functional analysis of nunF coupled with liquid chromatography-high-resolution mass spectrometry (LC-HRMS) showed that CLP biosynthesis is regulated by nunF. Quantitative real-time PCR analysis indicated that transcription of the NRPS genes catalyzing CLP production is strongly reduced when nunF is mutated indicating that nunF is part of the nun-nup regulon. Swarming and biofilm formation was reduced in a nunF knockout mutant suggesting that these CLPs may also play a role in these phenomena as observed in other pseudomonads. Fusion of the nunF promoter region to mCherry showed that nunF is strongly upregulated in response to carbon sources indicating the presence of a fungus suggesting that environmental elicitors may also influence nunF expression which upon activation regulates nunamycin and nunapeptin production required for the growth inhibition of phytopathogens.

General information
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Authors: Hennessy, R. C. (Ekstern), Phippen, C. (Intern), Nielsen, K. F. (Intern), Olsson, S. (Ekstern), Stougaard, P. (Ekstern)
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© 2017 The Authors. MicrobiologyOpen published by John Wiley & Sons Ltd.
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Biotechnological Applications of the Roseobacter Clade

The multitude of distinct niches that prevail in the marine environment has facilitated the development of very diverse marine microbiomes. This diversity is, naturally, reflected in their biochemistry and secondary metabolites and, hence, marine microbes represent a virtually untapped source of new bioactive compounds. The Roseobacter clade of marine α-proteobacteria represents some of the most abundant organisms in the marine environment and they may constitute as much as 20–30 % of the prokaryotic community during algal blooms. Often, they exhibit traits suggestive of a lifestyle in close association with phytoplankton; including traits related to surface colonization, iron scavenging, and the production of bioactive secondary metabolites. Despite the fact that relatively few bioactive compounds have been identified in the α-proteobacteria, the roseobacters are known to produce compounds capable of stimulating algae growth, i.e. auxins, and algaecidal compounds, i.e. the roseobacticides. In addition, the roseobacters can produce a range of antibacterial products, such as the small tropolone compound tropodithietic acid (TDA) and the nonribosomal peptide indigoidine. TDA targets a broad spectrum of Gram-positive and Gram-negative bacteria in which resistance towards the compound does not arise easily. Mining the genomes of roseobacters also reveal that they are likely capable of producing other compounds than hitherto discovered by classical bio-assay guided fractionation, since the genomes contain genes/gene clusters probably encoding unknown bioactive secondary metabolites. Therefore, bacteria of the Roseobacter clade may serve as potential sources of novel bioactive compounds, including novel antibiotics, which is of paramount importance in the battle against antibiotic resistant pathogenic bacteria.

The discovery of new antibiotic compounds is not the only means by which we can counter the spread of antibiotic resistance. Development of sustainable alternatives to the application of antibiotics in agri- and aquaculture may be equally important. Attributable to their inherent properties, the roseobacters may be such an alternative in the aquaculture industry. Especially at the younger stages in larviculture, disease outbreaks caused by fish pathogenic microorganisms may lead to mortality rates of 100 % when antibiotic treatment is not initiated. Adding roseobacters as probiotics is promising as fish larvae challenged with fish pathogens of the genus Vibrio exhibit survival rates similar to, or better than, unchallenged larvae when roseobacter probionts are added. Thus, the Roseobacter clade is a promising source of new bioactive compounds and a possible sustainable alternative to the prophylactic administration of antibiotics in fish rearing.

General information

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Authors: Bentzon-Tilia, M. (Intern), Gram, L. (Intern)
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DOIs: 10.1007/978-3-319-47935-4_7
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Breaking confinement: unconventional peptide presentation by major histocompatibility (MHC) class I allele HLA-A*02:01

Peptide antigen-presentation by Major Histocompatibility Class (MHC) I proteins initiates CD8+ T cell mediated immunity against pathogens and cancers. MHC I molecules typically bind peptides with nine amino acids in length with both ends tucked inside the major A and F binding pocket. It has been known for a while that longer peptides can also bind by either bulging out of the groove in the middle of the peptide or by binding in a zig-zag fashion inside the groove. In a recent study, we identified an alternative binding conformation of naturally occurring peptides from Toxoplasma gondii bound by HLA-A*02:01. These peptides were extended at the C-terminus (PΩ) and contained charged amino acids not more than 3 residues after the anchor amino acid at PΩ, which enabled them to open the F pocket and expose their C-terminal extension into the solvent. Here, we show that the mechanism of F pocket opening is dictated by the charge of the first charged amino acid found within the extension. While positively charged amino acid result in the Tyr84 swing, amino acids that are negatively charged induce a not previously described Lys146 lift. Further, we demonstrate that the peptides with alternative binding modes have properties that fit very poorly to the conventional MHC class I pathway, and suggest they are presented via alternative means, potentially including cross-presentation via the MHC class II pathway.

General information

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Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics
Pages: 5262-5270
Publication date: 2017
Butanol is cytotoxic to Lactococcus lactis while ethanol and hexanol are cytostatic

Lactic acid bacteria currently used extensively by the dairy industry have a superior tolerance towards small chain alcohols, which makes them interesting targets for use in future bio-refineries. The mechanism underlying the alcohol tolerance of lactic acid bacteria has so far received little attention. In the present study the physiological alcohol stress response of Lactococcus lactis subsp. cremoris MG1363 towards the primary, even-chain alcohols; ethanol, butanol, and hexanol was characterized. The alcohol tolerance of L. lactis was found comparable to those reported for highly alcohol resistant lactic acid bacteria. Combined results from alcohol survival rate, live/dead staining, and a novel usage of the beta-galactosidase assay, revealed that while high concentrations of ethanol and hexanol were cytostatic to L. lactis, high concentrations of butanol were cytotoxic, causing irreparable damages to the cell membrane.

General information
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Organisations: Department of Biotechnology and Biomedicine, Metabolic Signaling and Regulation, National Food Institute, Research Group for Microbial Biotechnology and Biorefining
Authors: Hviid, A. M. (Intern), Jensen, P. R. (Intern), Kilstrup, M. (Intern)
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Scopus rating (2014): SJR 1.461 SNIP 0.97 CiteScore 2.69
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.674 SNIP 1.028 CiteScore 3.34
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.6 SNIP 0.969 CiteScore 3.12
CASCADE, a platform for controlled gene amplification for high, tunable and selection-free gene expression in yeast

Over-expression of a gene by increasing its copy number is often desirable in the model yeast Saccharomyces cerevisiae. It may facilitate elucidation of enzyme functions, and in cell factory design it is used to increase production of proteins and metabolites. Current methods are typically exploiting expression from the multicopy 2μ-derived plasmid or by targeting genes repeatedly into sequences like Ty or rDNA; in both cases, high gene expression levels are often reached. However, with 2μ-based plasmid expression, the population of cells is very heterogeneous with respect to protein production; and for integration into repeated sequences it is difficult to determine the genetic setup of the resulting strains and to achieve specific gene doses. For both types of systems, the strains often suffer from genetic instability if proper selection pressure is not applied. Here we present a gene amplification system, CASCADE, which enables construction of strains with defined gene copy numbers. One or more genes can be amplified simultaneously and the resulting strains can be stably propagated on selection-free medium. As proof-of-concept, we have successfully used CASCADE to increase heterologous production of two fluorescent proteins, the enzyme β-galactosidase the fungal polyketide 6-methyl salicylic acid and the plant metabolite vanillin glucoside.

General information
State: Published
Cathepsin-S degraded decorin are elevated in fibrotic lung disorders - development and biological validation of a new serum biomarker

Background: Decorin is one of the most abundant proteoglycans of the extracellular matrix and is mainly secreted and deposited in the interstitial matrix by fibroblasts where it plays an important role in collagen turnover and tissue homeostasis. Degradation of decorin might disturb normal tissue homeostasis contributing to extracellular matrix remodeling diseases. Here, we present the development and validation of a competitive enzyme-linked immunosorbent assay (ELISA) quantifying a specific fragment of degraded decorin, which has potential as a novel non-invasive serum biomarker for fibrotic lung disorders.

Methods: A fragment of decorin cleaved in vitro using human articular cartilage was identified by mass-spectrometry (MS/MS). Monoclonal antibodies were raised against the neo-epitope of the cleaved decorin fragment and a competitive ELISA assay (DCN-CS) was developed. The assay was evaluated by determining the inter-and intra-assay precision, dilution recovery, accuracy, analyte stability and interference. Serum levels were assessed in lung cancer patients, patients with idiopathic pulmonary fibrosis (IPF), patients with chronic obstructive pulmonary disease (COPD) and healthy controls.

Results: The DCN-CS ELISA was technically robust and was specific for decorin cleaved by cathepsin-S. DCN-CS was elevated in lung cancer patients (p < 0.0001) and IPF patients (p < 0.001) when
compared to healthy controls. The diagnostic power for differentiating lung cancer patients and IPF patients from healthy controls was 0.96 and 0.77, respectively. Conclusion: Cathepsin-S degraded decorin could be quantified in serum using the DCN-CS competitive ELISA. The clinical data indicated that degradation of decorin by cathepsin-S is an important part of the pathology of lung cancer and IPF.

**General information**
State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Nordic Bioscience A/S, ProScion A/S, Janssen Pharmaceutical Companies
Authors: Kehlet, S. N. (Intern), Bager, C. L. (Ekstern), Willumsen, N. (Ekstern), Dasgupta, B. (Ekstern), Brodmerkel, C. (Ekstern), Curran, M. (Ekstern), Pedersen, S. B. (Intern), Leeming, D. J. (Ekstern), Karsdal, M. (Ekstern)
Number of pages: 10
Publication date: 2017
Main Research Area: Technical/natural sciences

**Publication information**
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.143 SJR 1.373
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.76 SJR 1.161 SNIP 1.125
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.048 SNIP 1.019 CiteScore 2.69
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.215 SNIP 1.196 CiteScore 2.97
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.151 SNIP 1.226 CiteScore 3.24
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.331 SNIP 1.489 CiteScore 3.41
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.295 SNIP 1.275 CiteScore 3.08
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.009 SNIP 1.031
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.911 SNIP 1.137
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.083 SNIP 0.832
Scopus rating (2007): SJR 0.589 SNIP 0.72
Scopus rating (2006): SJR 0.672 SNIP 0.591
Scopus rating (2005): SJR 0.283 SNIP 0.401
Scopus rating (2004): SJR 0.247 SNIP 0.346
Scopus rating (2003): SJR 0.211 SNIP 0.111
Scopus rating (2002): SJR 0.263 SNIP 0.085
Original language: English
Decorin, Cathepsin-S, Extracellular matrix, Cancer, Idiopathic pulmonary fibrosis, Serum biomarker
Electronic versions:
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**Bibliographical note**
Cell Factory Engineering
Rational approaches to modifying cells to make molecules of interest are of substantial economic and scientific interest. Most of these efforts aim at the production of native metabolites, expression of heterologous biosynthetic pathways, or protein expression. Reviews of these topics have largely focused on individual strategies or cell types, but collectively they fall under the broad umbrella of a growing field known as cell factory engineering. Here we condense >130 reviews and key studies in the art into a meta-review of cell factory engineering. We identified 33 generic strategies in the field, all applicable to multiple types of cells and products, and proven successful in multiple major cell types. These apply to three major categories: production of native metabolites and/or bioactives, heterologous expression of biosynthetic pathways, and protein expression. This meta-review provides general strategy guides for the broad range of applications of rational engineering of cell factories.

Characterization of a membrane-bound C-glucosyltransferase responsible for carminic acid biosynthesis in Dactylopius coccus Costa
Carminic acid, a glucosylated anthraquinone found in scale insects like Dactylopius coccus, has since ancient times been used as a red colorant in various applications. Here we show that a membrane-bound C-glucosyltransferase, isolated from D. coccus and designated DcUGT2, catalyzes the glucosylation of flavokermesic acid and kermesic acid into their respective C-glucosides dcII and carminic acid. DcUGT2 is predicted to be a type I integral endoplasmic reticulum (ER) membrane protein, containing a cleavable N-terminal signal peptide and a C-terminal transmembrane helix that anchors the protein to the ER, followed by a short cytoplasmic tail. DcUGT2 is found to be heavily glycosylated. Truncated DcUGT2 proteins synthesized in yeast indicate the presence of an internal ER-targeting signal. The cleavable N-terminal signal peptide is shown to be essential for the activity of DcUGT2, whereas the transmembrane helix/cytoplasmic domains, although important, are not crucial for its catalytic function.
Organisations: Department of Biotechnology and Biomedicine, Natural Product Discovery, Biosynthetic Pathway Engineering, University of Copenhagen, University of Southern Denmark, Chr. Hansen A/S

Authors: Kannangara, R. (Ekstern), Siukstaite, L. (Ekstern), Borch-Jensen, J. (Ekstern), Madsen, B. (Ekstern), Kongstad, K. T. (Ekstern), Staerk, D. (Ekstern), Bennedsen, M. (Ekstern), Okkels, F. T. (Ekstern), Rasmussen, S. A. (Intern), Larsen, T. O. (Intern), Frandsen, R. J. N. (Intern), Møller, B. L. (Ekstern)

Number of pages: 12
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Main Research Area: Technical/natural sciences

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BFI (2017): BFI-level 2
Scopus rating (2017): SNIP 2.912 SJR 6.582
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 11.8 SJR 6.414 SNIP 2.855
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 6.287 SNIP 2.86 CiteScore 11.23
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 6.41 SNIP 3.034 CiteScore 10.77
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 6.206 SNIP 2.797 CiteScore 9.85
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 5.866 SNIP 2.829 CiteScore 8.32
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 3.137 SNIP 1.825 CiteScore 4.44
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Original language: English

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Source: Findit
Source-ID: 2393878260

Publication: Research - peer-review › Journal article – Annual report year: 2017

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**Characterization of small-spored Alternaria from Argentinean crops through a polyphasic approach**

Small-spored Alternaria have been isolated from a wide variety of food crops, causing both economic losses and human health risk due to the metabolites produced. Their taxonomy has been discussed widely, but no scientific consensus has been established in this field to date. Argentina is a major exporter of agricultural products, so it is essential to thoroughly understand the physiological behaviour of this pathogen in a food safety context. Thus, the objective of this work was to characterize small-spored Alternaria spp. obtained from tomato fruits, pepper fruits, wheat grains and blueberries from Argentina by a polyphasic approach involving metabolomic and phylogenetic analyses based on molecular and morphological characters. Morphological analysis divided the population studied into three groups; A. arborescens sp.-
However, when these characters were simultaneously analysed with molecular data, no clearly separated groups were obtained. Haplotype network and phylogenetic analysis (both Bayesian and maximum parsimony) of a conserved region yielded the same result, suggesting that all isolates belong to the same species. Furthermore, no correlation could be established between morphological species-groups and a metabolite or group of metabolites synthesized. Thus, the whole set of analyses carried out in the present work supports the hypothesis that these small-spored Alternaria isolates from food belong to the same species. Identification at species level through classical morphology or modern molecular techniques does not seem to be a useful tool to predict toxicological risk in food matrices. The detection of any small-spored Alternaria from Section Alternaria (D.P. Lawr., Gannibal, Peever & B.M. Pryor 2013) in food implies a potential toxicological risk.
CHO glyco-engineering using CRISPR/Cas9 multiplexing for protein production with homogeneous N-glycan profiles

Combining the Chinese hamster ovary (CHO) - K1 draft genome1,2, identified CHO glycosyltransferases3 and the power of multiplexing gene knock-outs with CRISPR/Cas94 via co-transfection of Cas9 and one single guiding RNA (sgRNA) per target, we generated 20 Rituximab expressing CHO-S cell lines differing in amount and combination of insertions or deletions (indels) in the targeted genes. Clones harboring 9, 6 and 4 indels were further investigated for growth, Rituximab productivity and secretome N-glycosylation.

This resulted in clones with prolonged viabilities, no changes in N-glycan galactose contents but an increase of matured and sialylated N-glycan structures in the secretome. Additionally we point out, that multiplexing an increasing amount of genes most likely results in clones only revealing a few of all possible combinations of the targets and is highly driven by the sgRNA efficiency which can differ from each other by factor 4, even after FACS sorting.

General information

State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, CHO in Silico Engineering of Glycosylation and Protein Quality (CiSe), CHO Core, iLoop, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
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Main Research Area: Technical/natural sciences
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Clonality, virulence and antimicrobial resistance of enteroaggregative Escherichia coli from Mirzapur, Bangladesh

Purpose. This study investigates the virulence and antimicrobial resistance in association with common clonal complexes (CCs) of enteroaggregative Escherichia coli (EAEC) isolated from Bangladesh. The aim was to determine whether specific CCs were more likely to be associated with putative virulence genes and/or antimicrobial resistance. Methodology. The
presence of 15 virulence genes (by PCR) and susceptibility to 18 antibiotics were determined for 151 EAEC isolated from cases and controls during an intestinal infectious disease study carried out between 2007-2011 in the rural setting of Mirzapur, Bangladesh (Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH et al. Clin Infect Dis 2012; 55: S232-S245). These data were then analysed in the context of previously determined serotypes and clonal complexes defined by multi-locus sequence typing.

**Results.** Overall there was no association between the presence of virulence or antimicrobial resistance genes in isolates of EAEC from cases versus controls. However, when stratified by clonal complex (CC) one CC associated with cases harboured more virulence factors (CC40) and one CC harboured more resistance genes (CC38) than the average. There was no direct link between the virulence gene content and antibiotic resistance. Strains within a single CC had variable virulence and resistance gene content indicating independent and multiple gene acquisitions over time.

**Conclusion.** In Bangladesh, there are multiple clonal complexes of EAEC harbouring a variety of virulence and resistance genes. The emergence of two of the most successful clones appeared to be linked to either increased virulence (CC40) or antimicrobial resistance (CC38), but increased resistance and virulence were not found in the same clonal complexes.
Comments on "Screening and identification of novel ochratoxin A-producing fungi from grapes. Toxins 2016,8,833" - in reporting ochratoxin A production from strains of Aspergillus, Penicillium and talaromyces

Recently a species in the genus Talaromyces, a uniseriate species of Aspergillus section Nigri and an isolate each of two widespread species, Penicillium rubens and P. commune, were reported to produce ochratoxin A. This claim was based on insufficient biological and chemical data. We propose a list of criteria that need to be met before an unexpected mycotoxin producer is reported. There have only been convincing data on ochratoxin A production for Penicillium verrucosum, P. nordicum, P. thymicola, all from Penicillium series Verrucosa, and from species in three sections of Aspergillus: section Circumdati, section Nigri and section Flavi.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, National Research Council of Italy, CNR
Authors: Perrone, G. (Ekstern), Logrieco, A. F. (Ekstern), Frisvad, J. C. (Intern)
Number of pages: 5
Publication date: 2017
Main Research Area: Technical/natural sciences

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Journal: Toxins
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BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.136 SJR 0.955
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Comparative assessment of *Vibrio* virulence in marine fish larvae

Vibrionaceae infections are a major obstacle for marine larviculture; however, little is known about virulence differences of *Vibrio* strains. The virulence of *Vibrio* strains, mostly isolated from vibriosis outbreaks in farmed fish, was tested in larval challenge trials with cod (*Gadus morhua*), turbot (*Scophthalmus maximus*) and halibut (*Hippoglossus hippoglossus*) using a multiwell dish assays with single-egg/larvae cultures. The strains differed significantly in virulence as some caused a high mortality of larv reaching 100% mortality after a few days, while others had no or only marginal effects on survival. Some *Vibrio* strains were pathogenic in all of the larva species, while some caused disease only in one of the species. Twenty-nine of the *Vibrio anguillarum* strains increased the mortality of larvae from at least one fish species; however, pathogenicity of the strains differed markedly. Other *Vibrio* species had no or less pronounced effects on larval mortalities. Iron uptake has been related to *V. anguillarum* virulence; however, the presence or absence of the plasmid pJM1 encoding anguibactin did not correlate with virulence. The genomes of *V. anguillarum* were compared (D. Castillo, P.W. D’Alvise, M. Middelboe & L. Gram, unpublished data) and most of the high-virulent strains had acquired virulence genes from other pathogenic *Vibrio*.

**General information**

State: Published
Organisations: Department of Systems Biology, Bacterial Ecophysiology and Biotechnology, Department of Environmental Engineering, National Food Institute, Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, University of Copenhagen, University of Bergen, Fishlab, Institute of Marine Research
Authors: Rønneseth, A. (Ekstern), Castillo, D. (Ekstern), D’Alvise, P. (Intern), Tønnesen, Ø. (Ekstern), Haugland, G. (Ekstern), Grotkjær, T. (Intern), Engell-Sørensen, K. (Ekstern), Nørremark, L. (Ekstern), Bergh, Ø. (Ekstern), Wergeland, H. I. (Ekstern), Gram, L. (Intern)
Pages: 1373-1385
Publication date: 2017
Main Research Area: Technical/natural sciences

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Larval challenge, Vibrio anguillarum, Virulence

DOIs:
10.1111/jfd.12612

Publication: Research - peer-review › Journal article – Annual report year: 2017

Comparative Genome Analyses of Vibrio anguillarum Strains Reveal a Link with Pathogenicity Traits

Vibrio anguillarum is a marine bacterium that can cause vibriosis in many fish and shellfish species, leading to high mortalities and economic losses in aquaculture. Although putative virulence factors have been identified, the mechanism of pathogenesis of V. anguillarum is not fully understood. Here, we analyzed whole-genome sequences of a collection of V. anguillarum strains and compared them to virulence of the strains as determined in larval challenge assays. Previously identified virulence factors were globally distributed among the strains, with some genetic diversity. However, the pan-genome revealed that six out of nine high-virulence strains possessed a unique accessory genome that was attributed to pathogenic genomic islands, prophage-like elements, virulence factors, and a new set of gene clusters involved in biosynthesis, modification, and transport of polysaccharides. In contrast, V. anguillarum strains that were medium to nonvirulent had a high degree of genomic homogeneity. Finally, we found that a phylogeny based on the core genomes clustered the strains with moderate to no virulence, while six out of nine high-virulence strains represented phylogenetically separate clusters. Hence, we suggest a link between genotype and virulence characteristics of Vibrio anguillarum, which can be used to unravel the molecular evolution of V. anguillarum and can also be important from survey and diagnostic perspectives.

Importance: Comparative genome analysis of strains of a pathogenic bacterial species can be a powerful tool to discover acquisition of mobile genetic elements related to virulence. Here, we compared 28 V. anguillarum strains that differed in virulence in fish larval models. By pan-genome analyses, we found that six of nine highly virulent strains had a unique core
and accessory genome. In contrast, V. anguillarum strains that were medium to nonvirulent had low genomic diversity. Integration of genomic and phenotypic features provides insights into the evolution of V. anguillarum and can also be important for survey and diagnostic purposes.

**General information**
State: Published
Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, University of Copenhagen, BGI Park, China, Copenhagen Bio Science Park
Authors: Castillo, D. (Ekstern), D'Alvise, P. (Intern), Xu, R. (Ekstern), Zhang, F. (Ekstern), Middelboe, M. (Ekstern), Gram, L. (Intern)
Number of pages: 14
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Main Research Area: Technical/natural sciences

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Web of Science (2016): Indexed yes
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© 2017 Castillo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license
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Publication: Research - peer-review › Journal article – Annual report year: 2017

**Comparative Genomics of Bacteriophage of the Genus Seuratvirus**
Despite being more abundant and having smaller genomes than their bacterial host, relatively few bacteriophages have had their genomes sequenced. Here, we isolated 14 bacteriophages from cattle slurry and performed de novo genome sequencing, assembly, and annotation. The commonly used marker genes polB and terL showed these bacteriophages to be closely related to members of the genus Seuratvirus. We performed a core-gene analysis using the 14 new and four closely related genomes. A total of 58 core genes were identified, the majority of which has no known function. These genes were used to construct a core-gene phylogeny, the results of which confirmed the new isolates to be part of the genus Seuratvirus and expanded the number of species within this genus to four. All bacteriophages within the genus contained the genes queCDE encoding enzymes involved in queuosine biosynthesis. We suggest these genes are carried as a mechanism to modify DNA in order to protect these bacteriophages against host endonucleases.

**General information**
State: Published
Organisations: Department of Biotechnology and Biomedicine, Infection Microbiology, University of Warwick, University of Nottingham, University of Leicester
Authors: Sazinas, P. (Intern), Redgwell, T. (Ekstern), Rihtman, B. (Ekstern), Grigonyte, A. (Ekstern), Michniewski, S. (Ekstern), Scanlan, D. J. (Ekstern), Hobman, J. (Ekstern), Millard, A. (Ekstern)
Number of pages: 5
Pages: 72-76
Publication date: 2017
Main Research Area: Technical/natural sciences

**Publication information**
Journal: Genome Biology and Evolution
Volume: 10
Issue number: 1
Comparative genomics reveals high biological diversity and specific adaptations in the industrially and medically important fungal genus Aspergillus

Background:
The fungal genus Aspergillus is of critical importance to humankind. Species include those with industrial applications, important pathogens of humans, animals and crops, a source of potent carcinogenic contaminants of food, and an important genetic model. The genome sequences of eight aspergilli have already been explored to investigate aspects of fungal biology, raising questions about evolution and specialization within this genus.

Results:
We have generated genome sequences for ten novel, highly diverse Aspergillus species and compared these in detail to sister and more distant genera. Comparative studies of key aspects of fungal biology, including primary and secondary metabolism, stress response, biomass degradation, and signal transduction, revealed both conservation and diversity among the species. Observed genomic differences were validated with experimental studies. This revealed several highlights, such as the potential for sex in asexual species, organic acid production genes being a key feature of black aspergilli, alternative approaches for degrading plant biomass, and indications for the genetic basis of stress response. A genome-wide phylogenetic analysis demonstrated in detail the relationship of the newly genome sequenced species with other aspergilli.

Conclusions:
Many aspects of biological differences between fungal species cannot be explained by current knowledge obtained from genome sequences. The comparative genomics and experimental study, presented here, allows for the first time a genus-wide view of the biological diversity of the aspergilli and in many, but not all, cases linked genome differences to phenotype. Insights gained could be exploited for biotechnological and medical applications of fungi.
Comparative Genomics Reveals High Genomic Diversity in the Genus Photobacterium

Vibrionaceae is a large marine bacterial family, which can constitute up to 50% of the prokaryotic population in marine waters. Photobacterium is the second largest genus in the family and we used comparative genomics on 35 strains representing 16 of the 28 species described so far, to understand the genomic diversity present in the Photobacterium genus. Such understanding is important for ecophysiology studies of the genus. We used whole genome sequences to evaluate phylogenetic relationships using several analyses (16S rRNA, MLSA, fur, amino-acid usage, ANI), which allowed us to identify two misidentified strains. Genome analyses also revealed occurrence of higher and lower GC content clades, correlating with phylogenetic clusters. Pan-and core-genome analysis revealed the conservation of 25% of the genome throughout the genus, with a large and open pan-genome. The major source of genomic diversity could be traced to the smaller chromosome and plasmids. Several of the physiological traits studied in the genus did not correlate with phylogenetic data. Since horizontal gene transfer (HGT) is often suggested as a source of genetic diversity and a potential driver of genomic evolution in bacterial species, we looked into evidence of such in Photobacterium genomes. Genomic islands were the source of genomic differences between strains of the same species. Also, we found transposase genes and CRISPR arrays that suggest multiple encounters with foreign DNA. Presence of genomic exchange traits was widespread and abundant in the genus, suggesting a role in genomic evolution. The high genetic variability and indications of genetic exchange make it difficult to elucidate genome evolutionary paths and raise the awareness of the roles of foreign DNA in the genomic evolution of environmental organisms.
Comparative proteomics of oxidative stress response of Lactobacillus acidophilus NCFM reveals effects on DNA repair and cysteine de novo synthesis

Probiotic cultures encounter oxidative conditions during manufacturing, yet protein abundance changes induced by such stress have not been characterized for some of the most common probiotics and starters. This comparative proteomics investigation focuses on the response by Lactobacillus acidophilus NCFM to H2O2, simulating an oxidative environment. Bacterial growth was monitored by BioScreen and batch cultures were harvested at exponential phase for protein profiling.
of stress responses by 2D gel-based comparative proteomics. Proteins identified in 19 of 21 spots changing in abundance due to H2O2 were typically related to carbohydrate and energy metabolism, cysteine biosynthesis, and stress. In particular, increased cysteine synthase activity may accumulate a cysteine pool relevant for protein stability, enzyme catalysis and the disulfide-reducing pathway. The stress response further included elevated abundance of biomolecules reducing damage such as enzymes from DNA repair pathways and metabolic enzymes with active site cysteine residues. By contrast, a protein-refolding chaperone showed reduced abundance, possibly reflecting severe oxidative protein destruction that was not overcome by refolding. The proteome analysis provides novel insight into resistance mechanisms in lactic acid bacteria against reactive oxygen species and constitutes a valuable starting point for improving industrial processes, food design or strain engineering preserving microorganism viability.

General information
State: Published
Organisations: Enzyme and Protein Chemistry, Department of Biotechnology and Biomedicine, Immunoinformatics and Machine Learning, University of Torino
Authors: Calderini, E. (Ekstern), Celebioglu, H. U. (Intern), Villarroel, J. (Intern), Jacobsen, S. (Intern), Svensson, B. (Intern), Pessione, E. (Ekstern)
Number of pages: 10
Publication date: 2017
Main Research Area: Technical/natural sciences

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Journal: Proteomics
Volume: 17
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Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.85 SJR 1.564 SNIP 0.889
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.48 SNIP 0.969 CiteScore 3.7
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.449 SNIP 0.973 CiteScore 3.73
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.488 SNIP 0.978 CiteScore 3.88
ISI indexed (2013): ISI indexed yes
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BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.497 SNIP 1.094 CiteScore 4.1
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.691 SNIP 1.175 CiteScore 4.49
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.514 SNIP 1.123
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.518 SNIP 1.12
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Comparison of global gene expression profiles of microdissected human foetal Leydig cells with their normal and hyperplastic adult equivalents

STUDY QUESTION: Do human adult Leydig cells (ALCs) within hyperplastic micronodules display characteristics of foetal LCs (FLCs)?

SUMMARY ANSWER: The gene expression profiles of FLCs and all ALC subgroups were clearly different, but there were no significant differences in expressed genes between the normally clustered and hyperplastic ALCs.

WHAT IS KNOWN ALREADY: LCs are the primary androgen producing cells in males throughout development and appear in chronologically distinct populations; FLCs, neonatal LCs and ALCs. ALCs are responsible for progression through puberty and for maintenance of reproductive functions in adulthood. In patients with reproductive problems, such as infertility or testicular cancer, LC function is often impaired, and LCs may cluster abnormally into hyperplastic micronodules (defined as clusters of > 15 LCs in a cross-section).

STUDY DESIGN, SIZE, DURATION: A genome-wide microarray study of LCs microdissected from human foetal and adult tissue samples (n = 12). Additional tissue specimens (n = 15) were used for validation of the mRNA expression data at the protein level.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Frozen human tissue samples were used for the microarray study, including morphologically normal foetal (gestational week 10-11) testis samples, and adult testis specimens with normal LC distribution, LC micronodules or LC micronodules adjacent to hCG-producing testicular germ cell tumours. Transcriptome profiling was performed on Agilent whole human genome microarray 4 x 44 K chips. Microarray data pre-processing and statistical analysis were performed using the limma R/Bioconductor package in the R software, and differentially expressed genes were further analysed for gene set enrichment using the DAVID Bioinformatics software. Selected genes were studied at the protein level by immunohistochemistry.

MAIN RESULTS AND THE ROLE OF CHANCE: The transcriptomes of FLCs and ALCs differed significantly from each other, whereas the profiles of the normally clustered and hyperplastic ALCs were similar despite morphological heterogeneity. The study revealed several genes not known previously to be expressed in LCs during early development, including sulfotransferase family 2A member 1 (SULT2A1), WNT1-inducible signalling pathway protein 2 (WISP2), hydroxyprostaglandin dehydrogenase (HPGD) and insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), whose expression changes were validated at the protein level.

LARGE SCALE DATA: The transcriptomic data are deposited in ArrayExpress (accession code E-MTAB-5453).

LIMITATIONS, REASONS FOR CAUTION: The small number of biological replicates and the necessity of RNA amplification due to the scarcity of human tissues, especially foetal specimens, are the main limitations of the study. Heterogeneous subpopulations of LCs within micronodules were not discriminated during microdissection and might have affected the expression profiling. The study was constrained by the lack of availability of truly normal controls. Testis samples used as 'controls' displayed complete spermatogenesis and were from patients with germ cell neoplasia but with undetectable hCG and normal hormone levels.

WIDER IMPLICATIONS OF THE FINDINGS: The changes in LC morphology and function observed in patients with reproductive disorders possibly reflect subtle changes in the expression of many genes rather than regulatory changes of single genes or pathways. The study provides new insights into the development and maturation of human LCs by the identification of a number of potential functional markers for FLC and ALC.

General information
Conditions for mould growth on typical interior surfaces

Prediction of the risk for mould growth is an important parameter for the analysis and design of the hygrothermal performance of building constructions. However, in practice the mould growth does not always follow the predicted behavior described by the mould growth models. This is often explained by uncertainty in the real conditions of exposure. In this study, laboratory experiments were designed to determine mould growth at controlled transient climate compared to growth at constant climate. The experiment included three building materials with four different surface treatments. The samples were inoculated with 8 common indoor moulds. Even after 40 weeks no growth was observed on any sample. The paper describes different hypotheses for the missing growth, and how these have been tested.

General information
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Contamination of the Arctic reflected in microbial metagenomes from the Greenland ice sheet: Letter

Globally emitted contaminants accumulate in the Arctic and are stored in the frozen environments of the cryosphere. Climate change influences the release of these contaminants through elevated melt rates, resulting in increased contamination locally. Our understanding of how biological processes interact with contamination in the Arctic is limited. Through shotgun metagenomic data and binned genomes from metagenomes we show that microbial communities, sampled from multiple surface ice locations on the Greenland ice sheet, have the potential for resistance to and degradation of contaminants. The microbial potential to degrade anthropogenic contaminants, such as toxic and persistent polychlorinated biphenyls, was found to be spatially variable and not limited to regions close to human activities. Binned genomes showed close resemblance to microorganisms isolated from contaminated habitats. These results indicate that, from a microbiological perspective, the Greenland ice sheet cannot be seen as a pristine environment.

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Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
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Web of Science (2013): Indexed yes
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Scopus rating (2008): SJR 0.73 SNIP 1.208
Critical review on biofilm methods

Biofilms are widespread in nature and constitute an important strategy implemented by microorganisms to survive in sometimes harsh environmental conditions. They can be beneficial or have a negative impact particularly when formed in industrial settings or on medical devices. As such, research into the formation and elimination of biofilms is important for many disciplines. Several new methodologies have been recently developed for, or adapted to, biofilm studies that have contributed to deeper knowledge on biofilm physiology, structure and composition. In this review, traditional and cutting-edge methods to study biofilm biomass, viability, structure, composition and physiology are addressed. Moreover, as there is a lack of consensus among the diversity of techniques used to grow and study biofilms. This review intends to remedy this, by giving a critical perspective, highlighting the advantages and limitations of several methods. Accordingly, this review aims at helping scientists in finding the most appropriate and up-to-date methods to study their biofilms.
Cross-recognition of a pit viper (Crotalinae) polyspecific antivenom explored through high-density peptide microarray epitope mapping

Snakebite antivenom is a 120 years old invention based on polyclonal mixtures of antibodies purified from the blood of hyper-immunized animals. Knowledge on antibody recognition sites (epitopes) on snake venom proteins is limited, but may be used to provide molecular level explanations for antivenom cross-reactivity. In turn, this may help guide antivenom development by elucidating immunological biases in existing antivenoms. In this study, we have identified and characterized linear elements of B-cell epitopes from 870 pit vipers venom protein sequences by employing a high-throughput methodology based on custom designed high-density peptide microarrays. By combining data on antibody-peptide interactions with multiple sequence alignments of homologous toxin sequences and protein modelling, we have determined linear elements of antibody binding sites for snake venom metalloproteases (SVMPs), phospholipases A2s (PLA2s), and snake venom serine proteases (SVSPs). The studied antivenom antibodies were found to recognize linear elements in each of the three enzymatic toxin families. In contrast to a similar study of elapid (non-enzymatic) neurotoxins, these enzymatic toxins were generally not recognized at the catalytic active site responsible for toxicity, but instead at other sites, of which some are known for allosteric inhibition or for interaction with the tissue target. Antibody recognition was found to be preserved for several minor variations in the protein sequences, although the antibody-toxin interactions could often be eliminated completely by substitution of a single residue. This finding is likely to have large implications for the cross-reactivity of the antivenom and indicate that multiple different antibodies are likely to be needed for targeting an entire group of toxins in these recognized sites.
Data regarding the growth of Lactobacillus acidophilus NCFM on different carbohydrates and recombinant production of elongation factor G and pyruvate kinase.

The present study describes the growth of the very well-known probiotic bacterium Lactobacillus acidophilus NCFM on different carbohydrates. Furthermore, recombinant production of putative moonlighting proteins elongation factor G and pyruvate kinase from this bacterium is described. For further and detailed interpretation of the data presented here, please see the research article "Mucin- and carbohydrate-stimulated adhesion and subproteome changes of the probiotic bacterium Lactobacillus acidophilus NCFM" (Celebioglu et al., 2017) [1].
Delivery of TLR7 agonist to monocytes and dendritic cells by DCIR targeted liposomes induces robust production of anti-cancer cytokines

Tumor immune escape is today recognized as an important cancer hallmark and is therefore a major focus area in cancer therapy. Monocytes and dendritic cells (DCs), which are central to creating a robust anti-tumor immune response and establishing an anti-tumorigenic microenvironment, are directly targeted by the tumor escape mechanisms to develop immunosuppressive phenotypes. Providing activated monocytes and DCs to the tumor tissue is therefore an attractive way to break the tumor-derived immune suppression and reinstate cancer immune surveillance. To activate monocytes and DCs with high efficiency, we have investigated an immunotherapeutic Toll-Like Receptor (TLR) agonist delivery system comprising liposomes targeted to the dendritic cell immunoreceptor (DCIR). We formulated the immune stimulating TLR7 agonist TMX-202 in the liposomes and examined the targeting of the liposomes as well as their immune activating potential in blood-derived monocytes, myeloid DCs (mDCs), and plasmacytoid DCs (pDCs). Monocytes and mDCs were targeted with high specificity over lymphocytes, and exhibited potent TLR7-specific secretion of the anti-cancer cytokines IL-12p70, IFN-α 2α, and IFN-γ. This delivery system could be a way to improve cancer treatment either in the form of a vaccine with co-formulated antigen or as an immunotherapeutic vector to boost monocyte and DC activity in combination with other treatment protocols such as chemotherapy or radiotherapy. Cancer immunotherapy is a powerful new tool in the oncologist's therapeutic arsenal, with our increased knowledge of anti-tumor immunity providing many new targets for intervention. Monocytes and dendritic cells (DCs) are attractive targets for enhancing the anti-tumor immune response, but systemic delivery of immunomodulators has proven to be associated with a high risk of fatal adverse events due to the systemic activation of the immune system. We address this important obstacle by targeting the delivery of an immunomodulator, a Toll-like receptor agonist, to DCs and monocytes in the bloodstream. We thus focus the activation, potentially avoiding the above-mentioned adverse effects, and demonstrate greatly increased ability of the agonist to induce secretion of anti-cancer cytokines.
Development and application of computer-aided design methods for cell factory optimization

Genetically modified organisms (GMOs) can be used to produce chemicals for everyday applications. Engineering microorganisms is a multidisciplinary task comprising four steps: design, build, test and learn. The design and learn phases rely on computational, statistical models, data analysis and machine learning. The process of creating strains with commercially relevant titers is time consuming and expensive. Computer-aided design (CAD) software can help scientists build better strains by providing models and algorithms that can be used to generate and test hypotheses before implementing them in the lab.

Metabolic engineering already uses computational tools to design and analyze the metabolic and regulatory mechanisms of microorganisms. Genome-scale metabolic models (GEMs) describe the biochemical reactions in an organism and their relationship with the genome, hence they can be used to design microbial cell factories. In this PhD thesis we present cameo, a CAD software for metabolic engineering that uses GEMs. State-of-the-art and novel algorithms are implemented in cameo. These algorithms have been made accessible using a high-level API to enable any user to start running them without having advanced programming skills. Using cameo, we designed a Saccharomyces cerevisiae strain with improved mevalonate production.

In the food industry, recombinant DNA technologies cannot be used because of strict GMO regulations, especially in Europe. This industry relies on classical strain improvement (CSI) and adaptive laboratory evolution (ALE) to create new and better products. Nevertheless, some engineering and design principles can be applied to create strains in this industrial setup. In this work, we present MARSI, a software tool that uses a completely new model-based approach to strain design, focusing on metabolite targets. MARSI designs can be implemented using ALE or CSI.

We used MARSI to enumerate metabolite targets in Escherichia coli that could be used to replace experimentally validated gene knockouts.

Genetic variability occurs naturally in cells. However, the effects of those variations are unpredictable and can impact the performance of production strains. Moreover, strains resulting from CSI and ALE experiments contain a lot of mutations that are not trivial to explain. In this thesis, we explored strategies to integrate re-sequencing data using GEMs. Here, we present a workflow to integrate and analyze data from E. coli wild-type, mutant and closely related strains. In this study, we evaluated the effect of genetic variability on kcats. These parameters can be used to constrain GEMs and produce more accurate predictions. Therefore, using a combination of bioinformatics, chemoinformatics and machine learning tools, we explored the landscape of kcats using multiple enzyme sequences and their chemical reactions.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Global Econometric Modeling, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Research Groups, iLoop
Authors: Cardoso, J. (Intern), Andersen, M. R. (Intern), Herrgard, M. (Intern), Sonnenschein, N. (Intern)
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Development of a Bacterial Biosensor for Rapid Screening of Yeast p-Coumaric Acid Production

Transcription factor-based biosensors are used to identify producer strains, a critical bottleneck in cell factory engineering. Here, we address two challenges with this methodology: transplantation of heterologous transcriptional regulators into new hosts to generate functional biosensors and biosensing of the extracellular product concentration that accurately reflects the effective cell factory production capacity. We describe the effects of different translation initiation rates on the dynamic range of a p-coumaric acid biosensor based on the Bacillus subtilis transcriptional repressor PadR by varying its ribosomal binding site. Furthermore, we demonstrate the functionality of this p-coumaric acid biosensor in Escherichia coli and Corynebacterium glutamicum. Finally, we encapsulate yeast p-coumaric acid-producing cells with E. coli-biosensing cells in picoliter droplets and, in a microfluidic device, rapidly sort droplets containing yeast cells producing high amounts of extracellular p-coumaric acid using the fluorescent E. coli biosensor signal. As additional biosensors become available, such approaches will find broad applications for screening of an extracellular product.
Development of novel monoclonal antibodies against starch and ulvan - Implications for antibody production against polysaccharides with limited immunogenicity

Monoclonal antibodies (mAbs) are widely used and powerful research tools, but the generation of mAbs against glycan epitopes is generally more problematic than against proteins. This is especially significant for research on polysaccharide-rich land plants and algae (Viridiplantae). Most antibody production is based on using single antigens, however, there are significant gaps in the current repertoire of mAbs against some glycan targets with low immunogenicity. We approached mAb production in a different way and immunised with a complex mixture of polysaccharides. The multiplexed screening capability of carbohydrate microarrays was then exploited to deconvolute the specificities of individual mAbs. Using this strategy, we generated a set of novel mAbs, including one against starch (INCh1) and one against ulvan (INCh2). These polysaccharides are important storage and structural polymers respectively, but both are generally considered as having limited immunogenicity. INCh1 and INCh2 therefore represent important new molecular probes for Viridiplantae research. Moreover, since the α-(1-4)-glucan epitope recognised by INCh1 is also a component of glycogen, this mAb can also be used in mammalian systems. We describe the detailed characterisation of INCh1 and INCh2, and discuss the potential of a non-directed mass-screening approach for mAb production against some glycan targets.

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Discovery, cloning and characterisation of proline specific prolyl endopeptidase, a gluten degrading thermo-stable enzyme from *Sphaerobacter thermophilus*

Gluten free products have emerged during the last decades, as a result of a growing public concern and technological advancements allowing gluten reduction in food products. One approach is to use gluten degrading enzymes, typically at low or ambient temperatures, whereas many food production processes occur at elevated temperature. We present in this paper, the discovery, cloning and characterisation of a novel recombinant thermostable gluten degrading enzyme, a proline specific prolyl endoprotease (PEP) from *Sphaerobacter thermophilus*. The molecular mass of the prolyl endopeptidase was estimated to be 77 kDa by using SDS-PAGE. Enzyme activity assays with a synthetic dipeptide Z-Gly-Pro-p-nitroanilide as the substrate revealed that the enzyme had optimal activity at pH 6.6 and was most active from pH 5.0-8.0. The optimum temperature was 63 °C and residual activity after one hour incubation at 63 °C was higher than 75 %. The enzyme was activated and stabilized by Co2+ and inhibited by Mg2+, K+ and Ca2+ followed by Zn2+, Na+, Mn2+, Al3+, and Cu2+. The Km and kcat values of the purified enzyme for different substrates were evaluated. The ability to degrade immunogenic gluten peptides (POQPLPYPOQPLPY (α-gliadin) and SQOQFPQQPFQOPY (γ-hordein)) was also confirmed by enzymatic assays and mass spectrometric analysis of cleavage fragments. Addition of the enzyme during small scale mashing of barley malt reduced the gluten content. The findings here demonstrate the potential of enzyme use during mashing to produce gluten free beer, and provide new insights into the effects of proline specific proteases on gluten degradation.

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Web of Science (2015): Indexed yes
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Web of Science (2014): Indexed yes
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Discovery of Aspergillus frankstonensis sp nov during environmental sampling for animal and human fungal pathogens

Invasive fungal infections (IFI) due to species in Aspergillus section Fumigati (ASF), including the Aspergillus viridinutans species complex (AVSC), are increasingly reported in humans and cats. The risk of exposure to these medically important fungi in Australia is unknown. Air and soil was sampled from the domiciles of pet cats diagnosed with these IFI and from a nature reserve in Frankston, Victoria, where Aspergillus viridinutans sensu stricto was discovered in 1954. Of 104 ASF species isolated, 61% were A. fumigatus sensu stricto, 9% were AVSC (A. felis-clade and A. frankstonensis sp. nov.) and 30% were other species (30%). Seven pathogenic ASF species known to cause disease in humans and animals (A. felis-clade, A. fischeri, A. thermomutatus, A. lentulus, A. laciniosus A. fumisynne-matus, A. hiratsukae) comprised 25% of isolates overall. AVSC species were only isolated from Frankston soil where they were abundant, suggesting a particular ecological niche. Phylogenetic, morphological and metabolomic analyses of these isolates identified a new species, A. frankstonensis that is phylogenetically distinct from other AVSC species, hetero-thallic and produces a unique array of extrolites, including the UV spectrum characterized compounds DOLD, RAIMO and CALBO. Shared morphological and physiological characteristics with other AVSC species include slow sporulation, optimal growth at 37 °C, no growth at 50 °C, and viriditoxin production. Overall, the risk of environmental exposure to pathogenic species in ASF in Australia appears to be high, but there was no evidence of direct environmental exposure to AVSC species in areas where humans and cats cohabit.
Discovery of α-L-arabinopyranosidases from human gut microbiome expands the diversity within glycoside hydrolase family 42

Enzymes of the glycoside hydrolase family 42 (GH42) are widespread in bacteria of the human gut microbiome and play fundamental roles in the decomposition of both milk and plant oligosaccharides. All GH42 enzymes characterized so far have β-galactosidase activity. Here, we report the existence of a GH42 subfamily that is exclusively specific for α-L-arabinopyranoside and describe the first representative of this subfamily. We found that this enzyme (BlArap42B) from a probiotic Bifidobacterium species cannot hydrolyze β-galactosides. However, BlArap42B effectively hydrolyzed paeonolide and ginsenoside Rb2, plant glycosides containing an aromatic aglycone conjugated to α-L-arabinopyranosyl-(1,6)-β-D-glucopyranoside. Paeonolide, a natural glycoside from the roots of the plant genus Paeonia, is not hydrolyzed by classical GH42 β-galactosidases. X-ray crystallography revealed a unique Trp345-X12-Trp358 sequence motif at the BlArap42B active site, as compared to a Phe-X12-His motif in classical GH42 β-galactosidases. This analysis also indicated that the C6 position of galactose is blocked by the aromatic side chains, hence allowing accommodation only of Arap lacking this carbon. Automated docking of paeonolide revealed that it can fit into the BlArap42B active site. The Glcp moiety of paeonolide stacks onto the aromatic ring of the Trp252 at subsite +1 and C4-OH is hydrogen bonded with Asp249. Moreover, the aglycone stacks against Phe421 from the neighboring monomer in the BlArap42B trimer, forming a proposed subsite +2. These results further support the notion that evolution of metabolic specialization can be tracked at the structural level in key enzymes facilitating degradation of specific glycans in an ecological niche.
Diversity, Prevalence, and Longitudinal Occurrence of Type II Toxin-Antitoxin Systems of Pseudomonas aeruginosa Infecting Cystic Fibrosis Lungs

Type II toxin-antitoxin (TA) systems are most commonly composed of two genes encoding a stable toxin, which harms the cell, and an unstable antitoxin that can inactivate it. TA systems were initially characterized as selfish elements, but have recently gained attention for regulating general stress responses responsible for pathogen virulence, formation of drug-tolerant persister cells and biofilms—all implicated in causing recalcitrant chronic infections. We use a bioinformatics approach to explore the distribution and evolution of type II TA loci of the opportunistic pathogen, Pseudomonas.
aeruginosa, across longitudinally sampled isolates from cystic fibrosis lungs. We identify their location in the genome, mutations, and gain/loss during infection to elucidate their function(s) in stabilizing selfish elements and pathogenesis. We found (1) 26 distinct TA systems, where all isolates harbor four in their core genome and a variable number of the remaining 22 on genomic islands; (2) limited mutations in core genome TA loci, suggesting they are not under negative selection; (3) no evidence for horizontal transmission of elements with TA systems between clone types within patients, despite their ability to mobilize; (4) no gain and limited loss of TA-bearing genomic islands, and of those elements partially lost, the remnant regions carry the TA systems supporting their role in genomic stabilization; (5) no significant correlation between frequency of TA systems and strain ability to establish as chronic infection, but those with a particular TA, are more successful in establishing a chronic infection.

**General information**

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Draft Genome Sequence of *Acinetobacter johnsonii* C6, an Environmental Isolate Engaging in Interspecific Metabolic Interactions

*Acinetobacter johnsonii* C6 originates from creosote-polluted groundwater and performs ecological and evolutionary interactions with *Pseudomonas putida* in biofilms. The draft genome of *A. johnsonii* C6 is 3.7 Mbp and was shaped by mobile genetic elements. It reveals genes facilitating the biodegradation of aromatic hydrocarbons and resistance to antimicrobials and metals.

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Relations
Activities:
Tar-Eating Bacterial Duo may Transform Toxic Compounds into New Usable Materials
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Source-ID: 131476392
Publication: Research - peer-review › Journal article – Annual report year: 2017

Dual Amylin and Calcitonin Receptor Agonists: A Novel Treatment for Obesity and Related Co-Morbidities
Amylin and/or calcitonin receptor agonists such as pramlintide and davalintide have shown promise on weight reduction in preclinical models and clinical settings, albeit with limited efficacy on glucose homeostasis.

The overall aim of this Ph.D. project was to investigate the metabolic effect of the dual amylin and calcitonin receptor agonists (DACRA), KBP-042, KBP-088, KBP-089, focusing on the weight reducing and glucoregulatory potential in preclinical animal models of obesity and related morbidities like type 2 diabetes (T2D) and nonalcoholic steatohepatitis (NASH). Both synthetic and naturally occurring DACRAs exert prolonged receptor activation and it is hypothesized that this prolonged receptor activation will improve the in vivo efficacy. Furthermore, it is hypothesized that DACRAs have
beneficial metabolic effects beyond caloric intake and simple diet-induced weight loss.

In this series of studies, the focus was on metabolic effects of KBPs. Effects on body weight and adipose tissue as well as glucose metabolism were thoroughly explored in experimental rat models resembling the phenotypes of obesity, T2D and NASH, to address whether these beneficial effects were solely due to suppression of food intake and the subsequent weight loss. As amylin agonism induces a well-known anorexic effect at dose initiation, these studies also focused on different dosing regimens including dose escalation and dosing frequency. Finally, we compared KBPs to a second-generation amylinomimetic, davainaltide, and combination of KBPs with the GLP-1 analogue, liraglutide.

KBPs potently activated both the amylin and calcitonin receptors in vitro, and demonstrated a prolonged receptor activation when compared to second-generation amylinomimetic, davainaltide.

KBPs transiently suppressed caloric intake, and induced and sustained a dose-dependent weight loss compared to vehicle and pair-fed rats. Concomitantly, overall adiposity was decreased and obesity related adipocyte hypertrophy were improved – findings superior to the effects obtained with davainaltide treatment. The inappropriate high fat diet-induced lipid accumulation was eliminated by KBP treatment, and interestingly, KBPs alleviated hyperinsulinemia and improved glucose tolerance even with significantly lower insulin levels. KBP treatment increased the glucose infusion rate during a hyperinsulinemic euglycemic clamp indicating enhanced insulin action. Importantly, KBPs also improved glucose homeostasis and enhanced insulin action in Zucker Diabetic Fatty rats.

To investigate beneficial effects beyond weight loss, a weight-matched group was implemented. Of interest, weight matching led to improved glucose homeostasis through lowered plasma insulin; however, these were inferior to the effect of KBPs.

KBPs were introduced using various dosing regimens and frequencies. Dosing every day and every second day resulted in an equal weight loss at study end; however, with a later onset of maximal weight loss. To optimize tolerability, KBPs were introduced by dose escalation. In a 4-fold dose escalation, KBPs induced a transient reduction in food intake at every escalation step – with reducing magnitude over time. Two-fold and linear escalations suppressed body weight evenly with no significant reduction in food intake at either escalation step; however, with a delayed onset of maximum efficacy.

Interestingly, when KBP and liraglutide were combined, the effect on acute food intake was superior to either of peptides as single-dose. Chronically, KBP-089 (1.25 μg/kg) and liraglutide (50 μg/kg) lowered body weight 8% and 2% in HFD rats, respectively, while the combination resulted in a 12% body weight reduction. Moreover, the combination improved glucose tolerance.

In a rat model resembling the phenotype of human NASH, KBP treatment led to a reduction of the high fat, high cholesterol and cholate diet induced increase in liver weight and circulating aspartate transaminase (AST) levels. Finally, at the histological level KBP treatment reduced hepatic steatosis, ballooning and inflammation, hence resulting in a reduced NAS score in combination with a lowered fibrosis stage.

In conclusion, KBPs induce and sustain weight loss, leading to improved metabolic parameters including food preference, and these are beyond those observed simply by dietinduced weight loss. Additionally, these peptides are well tolerated when introduced by dose escalation. Finally, KBPs reduce liver steatosis in both obese and NASH rats, and importantly reduced inflammation and fibrosis scores in NASH, hence underscoring the DACRA potential as an anti-obesity agent with benefits on glucose control and NASH.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Systems Metabolic Lipidology, Protein Glycoscience and Biotechnology, Nordic Bioscience A/S
Authors: Gydesen, S. (Intern), Hellgren, L. (Intern), Abou Hachem, M. (Intern), Henriksen, K. (Ekstern)
Number of pages: 137
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Publication: Research › Ph.D. thesis – Annual report year: 2017
Editorial: 3Rs tightly intertwined to maintain genome stability

DNA recombination, repair and replication are three large and vibrant research fields where each ‘R’ could deserve a series of reviews in its own right. However, as the 3Rs are tightly interwoven processes, one R can often not be fully understood without including the others. For example, replication of damaged DNA results in stalled replication forks that await DNA damage repair before replication can be resumed. In turn, the repair of most lesions depends on processes involving DNA synthesis. At the same time, the stalled forks may engage in recombination, either as part of a controlled repair process or by accident, just because it can, with the risk of producing genome rearrangements and loss of heterozygosity. The set of reviews presented in this thematic issue (https://academic-oup-com.proxy.findit.dtu.dk/femsyr/pages/replication_recombination_and_repair) of FEMS YR has been selected to highlight the intricate connections between the three Rs.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Eukaryotic Molecular Cell Biology, University of Copenhagen
Authors: Lisby, M. (ed.) (Ekstern), Mortensen, U. H. (ed.) (Intern)
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BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.51 SJR 1.254 SNIP 0.855
Web of Science (2016): Indexed yes
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Scopus rating (2015): SJR 1.196 SNIP 0.741 CiteScore 2.56
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.076 SNIP 0.831 CiteScore 2.37
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.248 SNIP 0.863 CiteScore 2.5
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.192 SNIP 0.841 CiteScore 2.56
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.221 SNIP 1.018 CiteScore 2.54
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.043 SNIP 0.92
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.977 SNIP 0.814
BFI (2008): BFI-level 1
Effect of repeat unit structure and molecular mass of lactic acid bacteria hetero-exopolysaccharides on binding to milk proteins

Interactions of exopolysaccharides and proteins are of great importance in food science, but complicated to analyze and quantify at the molecular level. A surface plasmon resonance procedure was established to characterize binding of seven structure-determined, branched hetero-exopolysaccharides (HePSs) of 0.14–4.9 MDa from lactic acid bacteria to different milk proteins (β-casein, κ-casein, native and heat-treated β-lactoglobulin) at pH 4.0–5.0. Maximum binding capacity (RUmax) and apparent affinity (KA,app) were HePS- and protein-dependent and varied for example 10- and 600-fold, respectively, in the complexation with native β-lactoglobulin at pH 4.0. Highest RUmax and KA,app were obtained with heat-treated β-lactoglobulin and β-casein, respectively. Overall, RUmax and KA,app decreased 6- and 20-fold, respectively, with increasing pH from 4.0 to 5.0. KA,app was influenced by ionic strength and temperature, indicating that polar interactions stabilize HePS–protein complexes. HePS size as well as oligosaccharide repeat structure, conferring chain flexibility and hydrogen bonding potential, influence the KA,app.
We report effects of dissolved oxygen (DO) concentration and iron addition on gene expression of Magnetospirillum gryphiswaldense MSR-1 cells during fermentations, focusing on 0.25-24 h after iron addition. The DO was strictly controlled at 0.5% or 5% O2, and compared with aerobic condition. Uptake of iron (and formation of magnetosomes) was only observed in the 0.5% O2 condition where there was little difference in cell growth and carbon consumption compared to the 5% O2 condition. Quantitative reverse transcription PCR analysis showed a rapid (within 0.25 h) genetic response of MSR-1 cells after iron addition for all the genes studied, except for MgFnr (oxygen sensor gene) and fur (ferric uptake regulator family gene), and which in some cases was oxygen-dependent. In particular, expression of sodB1 (superoxide dismutase gene) and feoB1 (ferrous transport protein B1 gene) were markedly reduced in cultures at 0.5% O2 compared to those at higher oxygen tensions. Moreover, expression of katG (catalase-peroxidase gene) and feoB2 (ferrous transport protein B2 gene) was reduced markedly by iron addition, regardless of oxygen conditions. The data provides a greater understanding of molecular response of MSR-1 cells to environmental conditions associated with oxygen and iron.
metabolisms, especially relevant to immediate-early stage of fermentation.

**General information**

State: Published
Organisations: National Food Institute, Research Group for Microbial Biotechnology and Biorefining, Center for Electron Nanoscopy, Department of Systems Biology, Department of Biotechnology and Biomedicine, Eukaryotic Molecular Cell Biology
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Scopus rating (2017): SNIP 0.58 SJR 0.79
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.76 SJR 0.842 SNIP 0.615
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.156 SNIP 0.756 CiteScore 2.08
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.136 SNIP 0.767 CiteScore 2.17
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.053 SNIP 0.719 CiteScore 2.25
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.073 SNIP 0.804 CiteScore 2.25
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.105 SNIP 0.764 CiteScore 2.26
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.081 SNIP 0.754
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.13 SNIP 0.834
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.084 SNIP 0.834
Scopus rating (2007): SJR 1.103 SNIP 0.864
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.105 SNIP 0.86
Effects of gamma irradiation and comparison of different extraction methods on sesquiterpene lactone yields from the medicinal plant Thapsia garganica L. (Apiaceae)

Ethnopharmacological relevance: Thapsia garganica L. roots are used in Algerian traditional medicine for a number of ailments. It is used in a poultice as an antitussive treatment of acute bronchitis and pneumonia, in preparations with milk or oil taken orally to treat common lung diseases, and with the direct application of root sections for the soothing of dental pains. Aim of the study: The objective of this study was to evaluate the combined effect of microwave assisted extraction and gamma irradiation on sesquiterpene lactones in T. garganica extracts. Materials and methods: To evaluate the combined effect of microwave assisted extraction and gamma irradiation on the highly bioactive compounds found in extracts of Algerian T. garganica, samples from different locations in Algeria were prepared by extraction from dried leaf and root samples of dried plant material, using different extraction methods. Quantification of the compounds of interest was done using an HPLC. The antioxidant activity extracts was determined using the two free radical scavenging assays: the 2,2-diphenyl-picryl-hydrazyl (DPPH) and the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt (ABTS). Results: It was found that location and extraction method had significant impact on the phytochemical composition of extracts. Gamma irradiation was found to have no effect on the phytochemical composition of the plant extracts or on their antioxidant properties. Conclusion: The study has shown that microwave assisted extraction is an effective method for investigating chemical compounds in T. garganica and the results support the notion that gamma irradiation for sterilisation do not alter the chemical composition. The authors wish to clarify that we cannot recommend the usage of any parts of T. garganica, in any form, for any remedy due to its very high toxicity.

General information
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Organisations: Department of Biotechnology and Biomedicine, Photosynthetic Cell Factories, National School Agronomic (ENSA), University of Copenhagen, University of Sciences and Technology Houari Boumediene
Authors: Mohamed Ibrahim, A. M. (Ekstern), Martinez-Swatson, K. A. (Ekstern), Benkaci-Ali, F. (Ekstern), Cozzi, F. (Ekstern), Zoulikha, F. (Ekstern), Simonsen, H. T. (Intern)
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Scopus rating (2017): SNIP 1.007 SJR 0.355
Scopus rating (2016): CiteScore 0.88 SNIP 0.672 SJR 0.231
Scopus rating (2015): CiteScore 0.7 SNIP 0.62 SJR 0.24
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Antioxidant, Gamma irradiation, Microwave assisted extraction, Thapsia garganica, Thapsigargin
Effects of gelling agent and extracellular signaling molecules on the culturability of marine bacteria

Only 1% of marine bacteria are currently culturable using standard laboratory procedures and this is a major obstacle for our understanding of the biology of marine microorganisms and for the discovery of novel microbial natural products. Therefore, the purpose of the present study was to investigate if improved cultivation conditions, including the use of an alternative gelling agent, and supplementation with signaling molecules, could improve the culturability of bacteria from seawater. Substituting agar with gellan gum improved viable counts 3–40-fold, depending on medium composition and incubation conditions, with a maximum of 6.6% culturability relative to direct cell counts. Through V4 amplicon sequencing we found that culturable diversity was also affected by a change in gelling agent, facilitating the growth of orders not culturable on agar-based substrates. Community analyses showed that communities grown on gellan gum substrates were significantly different from communities grown on agar, and that they covered a larger fraction of the seawater community. Other factors, such as incubation temperature and time, had less obvious effects on viable counts and culturable diversity. Supplementation with acyl homoserine lactones (AHLs) did not have a positive effect on total viable counts and no strong effect on culturable diversity. However, low concentrations of AHLs did increase the relative abundance of Sphingobacteria. Hence, with alternative growth substrates it is possible to significantly increase the number and diversity of cultured marine bacteria.

General information
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Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, DTU Metabolomics Core, Bacterial Ecophysiology and Biotechnology
Authors: Rygaard, A. M. (Intern), Schmidt Thøgersen, M. (Intern), Nielsen, K. F. (Intern), Gram, L. (Intern), Bentzon-Tilia, M. (Intern)
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Main Research Area: Technical/natural sciences

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Scopus rating (2016): CiteScore 4.08
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.891 SNIP 1.308 CiteScore 4.14
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.857 SNIP 1.384 CiteScore 4.02
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.899 SNIP 1.414 CiteScore 4.25
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 1.975 SNIP 1.429 CiteScore 4.29
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Effects of Gliadin consumption on the Intestinal Microbiota and Metabolic Homeostasis in Mice Fed a High-fat Diet

Dietary gluten causes severe disorders like celiac disease in gluten-intolerant humans. However, currently understanding of its impact in tolerant individuals is limited. Our objective was to test whether gliadin, one of the detrimental parts of gluten, would impact the metabolic effects of an obesogenic diet. Mice were fed either a defined high-fat diet (HFD) containing 4% gliadin (n=20), or a gliadin-free, isocaloric HFD (n=20) for 23 weeks. Combined analysis of several parameters including insulin resistance, histology of liver and adipose tissue, intestinal microbiota in three gut compartments, gut barrier function, gene expression, urinary metabolites and immune profiles in intestinal, lymphoid, liver and adipose tissues was performed. Mice fed the gliadin-containing HFD displayed higher glycated hemoglobin and higher insulin resistance as evaluated by the homeostasis model assessment, more hepatic lipid accumulation and smaller adipocytes than mice fed the gliadin-free HFD. This was accompanied by alterations in the composition and activity of the gut microbiota, gut barrier function, urine metabolome, and immune phenotypes within liver and adipose tissue. Our results reveal that gliadin disturbs the intestinal environment and affects metabolic homeostasis in obese mice, suggesting a detrimental effect of gluten intake in gluten-tolerant subjects consuming a high-fat diet.
Elucidating the biosynthetic pathway of the anticancer secondary metabolite calbistrin in Penicillium decumbens

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Organisations: Department of Biotechnology and Biomedicine, Biosynthetic Pathway Engineering, Natural Product Discovery, Fungal Chemodiversity, Department of Biotechnology, University of Groningen, Chalmers University of Technology
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Publication date: 2017
Event: Abstract from 29th Fungal Genetics Conference, Pacific Grove, United States.
Elucidating the Molecular Factors Implicated in the Persistence and Evolution of Transferable Antibiotic Resistance

Being the most diverse and abundant domain of life, bacteria exemplify the remarkable ability of evolution to fit organisms into almost any imaginable niche on the planet. Although the capacity of bacteria to diversify and adapt is fundamental to natural ecosystems and modern biotechnology, the same adaptive mechanisms constantly threaten human health. Less than a century ago, infectious disease was among the most common causes of mortality, but luckily this situation was drastically improved with the introduction of vaccination and effective antimicrobial drugs. Unfortunately, this situation is changing with the rapid emergence of multidrug resistant bacteria that do not respond to our current treatments. This process is to a large extent driven by gene exchange that allows bacteria to rapidly acquire ready-made adaptive features. The aim of this thesis has been to understand the adaptive mechanisms governing the dynamics of bacterial gene-sharing. Specifically, the focus has been on antibiotic resistance genes and their genetic vectors due to the profound implications of these genetic elements in human health. To observe the extend and impact of gene transfer events in a highly relevant natural environment, we looked into the genomes of Escherichia coli longitudinally sampled from the infant gut over the first year of life. Sequence analysis revealed a high degree of genomic plasticity, with frequent gene acquisition and loss events. While the acquisition of new genetic material is often deleterious, we show that plasmids encoding resistance and virulence factors may indeed be stably maintained in the gut despite imposing a measurable fitness cost to their bacterial hosts in vitro. In two studies investigating the stability of genetic elements, we zoom in on the molecular mechanisms enabling conflict resolution between incoming genetic elements and naïve recipient genomes. In both studies, the burden of initially costly genetic elements is ameliorated via adaptive evolution over time. In the case of a large multi-drug resistance plasmid, adaptation happens through IS26 mediated deletions of costly genes that (collaterally) sacrifice the transfer proficiency of the plasmid. For the industrially relevant mevalonate production pathway, we observe similar population-level loss dynamics. Using ultra-deep sequencing we show that the cost-attenuated pathway variants are interrupted by different IS-element insertions that enrich over time due to the fitness benefit of production loss. For both studies, the compensatory activity depends on the host background, and we suggest measures that can harness evolution to increase genetic stability of the costly production pathway. The final study of this thesis investigates the phenotypic effects of expressing 200 antibiotic resistance genes in E. coli. As the currency of evolution, genes are subject to selection at different levels that may promote or limit their success when transferred to a new host. Through sequence analysis and experimental interrogations, we suggest that functional constrains, rather than sequence composition, is the main challenge that acquired genes encounter when transferred across phylogeny. The work conducted in this thesis provides novel insight into the persistence and evolution of highly relevant genetic elements in vitro, in vivo and in situ. The conclusions shed light on fundamental evolutionary questions of genome dynamics and bacterial adaptation, which may ultimately improve our ability to predict and prevent the spread of antibiotic resistance and guide the engineering of robust biological systems.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Department of Biotechnology and Biomedicine, Infection Microbiology
Authors: Porse, A. (Intern), Sommer, M. O. A. (Intern), Jelsbak, L. (Intern), Munck, C. (Intern)
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Relations
Projects:
Elucidating the Molecular Factors Implicated in the Persistence and Evolution of Transferable Antibiotic Resistance
Publication: Research › Ph.D. thesis – Annual report year: 2018

Engineering of secondary metabolite production in streptomycetes
Streptomycetes are known for their ability to produce a range of different secondary metabolites, including antibiotics, immunosuppressive, anti-fungals, and anti-cancer compounds. Of these compounds, antibiotics play an important role in the clinics for treatment of both mild and severe bacterial infections. However, with the rise of multi-resistant pathogens, the demand for new antibiotics or derivatives of old ones, with improved properties, is now higher than ever. Recent efforts in genome sequencing and mining have revealed a so far untapped potential of streptomycetes and related actinomycetes
as evident from so-called “silent” biosynthetic gene clusters, whose products remain undetectable under standard laboratory conditions. These clusters harbour all information necessary for production of potentially novel bioactive compounds, and hence provide high priority candidates for engineering to activate their production. With this knowledge, the need for better molecular tools to harness the potential of the gifted microorganisms is now greater than ever. One such molecular tool, which has truly revolutionised the field of genome engineering, is the CRISPR-Cas9 genome engineering system. In this thesis, the CRISPR-Cas9 system for genome engineering of actinomycetes was expanded for future applications in a high-throughput semi-automatic setting. First, a toolbox and workflow for construction of CRISPR plasmids, for a range of different engineering purposes was developed, including the computational prediction of suitable 20 bp protospacers for the single guide RNAs and a USER-cloning method for construction of the CRISPR plasmids. Additional improvement to the system was achieved through the development of an optimised USER assembly workflow for cheaper and faster plasmid construction. The workflow was verified by manual knock-down of two biosynthetic gene clusters in model organism Streptomyces coelicolor A3(2), which confirmed the applicability of the system. A second part of the thesis was devoted to engineering of Streptomyces collinus Tü 365, which is a known producer of the narrow-spectrum antibiotic kirromycin. While there exists several studies addressing the PKS scaffold biosynthesis of kirromycin, knowledge about the supply of the precursor ethylmalonyl-CoA and most of the tailoring reactions remained scarce. In this thesis, the role of the gene kirN, believed to be involved in precursor supply, and the six genes kirM, kirHIV, kirHVI, kirOI and kirOII, all predicted to be involved in tailoring reactions, were investigated by gene inactivations, complementations, and characterisation of the biosynthetic products of the generated mutants. Within our studies, four novel kirromycin derivatives were generated and characterised. Our investigations allowed for closing some of the missing gaps in the biosynthesis of kirromycin, along with providing us with a toolbox of new mutants, which produce derivatives of the original compound. These derivatives could serve as scaffolds for future bioderivatization efforts. This thesis lays the groundwork for future engineering of streptomycetes to improve secondary metabolite production. For the USER-CRISPR-Cas9 platform, the next logical step will be to implement the workflow in a robotic setting. Furthermore, the mutants of S. collinus Tü 365 will be included in a derivatization platform to produce new kirromycin analogues with improved pharmacokinetic properties.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology
Authors: Robertsen, H. L. (Intern), Weber, T. (Intern), Gram, L. (Intern)
Number of pages: 170
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Relations
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Engineering of secondary metabolite production in streptomycetes
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Erratum to: SWITCH: a dynamic CRISPR tool for genome engineering and metabolic pathway control for cell factory construction in Saccharomyces cerevisiae
Upon publication of this article [1], it was brought to our attention that Figure 3 contained the following errors:

General information
State: Published
Organisations: Department of Systems Biology, Eucaryotic Molecular Cell Biology, Department of Biotechnology and Biomedicine, Eukaryotic Molecular Cell Biology, Roskilde University
Authors: Garcia Vanegas, K. (Intern), Lehka, B. J. (Ekstern), Mortensen, U. H. (Intern)
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Publication date: 2017
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Volume: 16
Article number: 53
Establishment of a Human Synovium and Cartilage Co-culture

General information
State: Published
Organisations: DTU Proteomics Core, Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Nordic Bioscience AS, Gentofte University Hospital
Authors: Kjelgaard-Petersen, C. F. (Intern), Bay-Jensen, A. (Ekstern), Christiansen, T. (Ekstern), Karsdal, M. (Ekstern), Hägglund, P. (Intern), Siebuhr, A. S. (Ekstern), Thudium, C. S. (Ekstern)
Number of pages: 2
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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.896 SJR 2.497
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.62 SJR 2.267 SNIP 1.8
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.325 SNIP 1.698 CiteScore 4.57
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.29 SNIP 1.655 CiteScore 4.19
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.4 SNIP 1.779 CiteScore 4.74
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.006 SNIP 1.658 CiteScore 4.12
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.035 SNIP 1.564 CiteScore 3.99
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.852 SNIP 1.604
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.797 SNIP 1.534
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.723 SNIP 1.452
Scopus rating (2007): SJR 1.768 SNIP 1.426
Scopus rating (2006): SJR 1.483 SNIP 1.515
Scopus rating (2005): SJR 1.827 SNIP 1.708
Scopus rating (2004): SJR 1.433 SNIP 1.445
Scopus rating (2003): SJR 1.272 SNIP 1.153
Scopus rating (2002): SJR 1.175 SNIP 1.022
Scopus rating (2001): SJR 0.998 SNIP 1.094
Scopus rating (2000): SJR 0.526 SNIP 1.183
Scopus rating (1999): SJR 0.806 SNIP 0.535
Original language: English
DOIs:
10.1016/j.joca.2017.02.468
Source: FindIt
Source-ID: 2356849782
Publication: Research - peer-review › Conference abstract in journal – Annual report year: 2017
Evolutionary analysis of whole-genome sequences confirms inter-farm transmission of Aleutian mink disease virus

Aleutian mink disease virus (AMDV) is a frequently encountered pathogen associated with mink farming. Previous phylogenetic analyses of AMDV have been based on shorter and more conserved parts of the genome, e.g. the partial NS1 gene. Such fragments are suitable for detection but are less useful for elucidating transmission pathways while sequencing entire viral genomes provides additional informative sites and often results in better-resolved phylogenies. We explore how whole-genome sequencing can benefit investigations of AMDV transmission by reconstructing the relationships between AMDV field samples from a Danish outbreak. We show that whole-genome phylogenies are much better resolved than those based on the partial NS1 gene sequences extracted from the same alignment. Well-resolved phylogenies contain more information about the underlying transmission trees and are useful for understanding the spread of a pathogen. In the main case investigated here, the transmission path suggested by the tree structure was supported by epidemiological data. The use of molecular clock models further improved tree resolution and provided time estimates for the viral ancestors consistent with the proposed direction of spread. It was however impossible to infer transmission pathways from the partial NS1 gene tree, since all samples from the case farms branched out from a single internal node. A sliding window analysis showed that there were no shorter genomic regions providing the same phylogenetic resolution as the entire genome. Altogether, these results suggest that phylogenetic analyses based on whole-genome sequencing taking into account sampling dates and epidemiological data is a promising set of tools for clarifying AMDV transmission.

General information
State: Published
Organisations: Molecular Evolution, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, National Veterinary Institute, Virology, Kopenhagen Fur
Authors: Hagberg, E. E. (Intern), Pedersen, A. G. (Intern), Larsen, L. E. (Intern), Krarup, A. (Ekstern)
Pages: 1360-1371
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Journal of General Virology
Volume: 98
Issue number: 6
ISSN (Print): 0022-1317
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.877 SJR 1.325
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.93 SJR 1.544 SNIP 0.891
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.738 SNIP 0.998 CiteScore 3.26
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.69 SNIP 1.057 CiteScore 3.25
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.764 SNIP 1.154 CiteScore 3.64
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.525 SNIP 1.034 CiteScore 3.28
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 1.684 SNIP 1.145 CiteScore 3.6
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Exo- and surface proteomes of the probiotic bacterium Lactobacillus acidophilus NCFM

Lactobacillus acidophilus NCFM is a well-known probiotic bacterium extensively studied for its beneficial health effects. Exoproteome (proteins exported into culture medium) and surface proteome (proteins attached to S-layer) of this probiotic were identified by using 2DE followed by MALDI TOF MS to find proteins potentially involved in bacteria-host interactions. The exo- and surface proteomes included 43 and 39 different proteins from 72 and 49 successfully identified spots, respectively. Twenty-two proteins were shared between the two proteomes; both contained the major surface layer protein that participates in host interaction as well as several well-known and putative moonlighting proteins. The exoproteome contained 9 classically-secreted (containing a signal sequence) and 10 non-classically secreted proteins, while the surface proteome contained four classically-secreted and 8 non-classically secreted proteins. Identification of exo- and surface proteomes contributes describing potential protein-mediated probiotic-host interactions.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry
Authors: Celebioglu, H. U. (Intern), Svensson, B. (Intern)
Number of pages: 16
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Proteomics
Volume: 17
Issue number: 11
Article number: 1700019
ISSN (Print): 1615-9853
Expansions and reductions in fungal primary metabolism studied across 100 fungal species

**General information**
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Brandl, J. (Intern), Rasmussen, J. L. N. (Intern), Vesth, T. C. (Intern), Andersen, M. R. (Intern)
Number of pages: 1
Publication date: 2017
Event: Abstract from 29th Fungal Genetics Conference, Pacific Grove, United States.
Main Research Area: Technical/natural sciences
Electronic versions:
Expansions and reductions in fungal primary metabolism studied across 100 fungal species
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

Exploration of immunoglobulin transcriptomes from mice immunized with three-finger toxins and phospholipases A2 from the Central American coral snake, Micrurus nigrocinctus

Snakebite envenomings represent a neglected public health issue in many parts of the rural tropical world. Animal-derived antivenoms have existed for more than a hundred years and are effective in neutralizing snake venom toxins when timely administered. However, the low immunogenicity of many small but potent snake venom toxins represents a challenge for obtaining a balanced immune response against the medically relevant components of the venom. Here, we employ high-throughput sequencing of the immunoglobulin (Ig) transcriptome of mice immunized with a three-finger toxin and a phospholipase A2 from the venom of the Central American coral snake, *Micrurus nigrocinctus*. Although exploratory in nature, our preliminary results showed that only low frequencies of mRNA encoding IgG isotypes, the most relevant isotype for therapeutic purposes, were present in splenocytes of five mice immunized with 6 doses of the two types of toxins over 90 days. Furthermore, analysis of Ig heavy chain transcripts showed that no particular combination of variable (V) and joining (J) gene segments had been selected in the immunization process, as would be expected after a strong humoral immune response to a single antigen. Combined with the titration of toxin-specific antibodies in the sera of immunized mice, these data support the low immunogenicity of three-finger toxins and phospholipases A2 found in *M. nigrocinctus* venoms, and highlight the need for future studies analyzing the complexity of antibody responses to toxins at the molecular level.

**General information**
State: Published
Organisations: Network Engineering of Eukaryotic Cell factories, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Genomic Epidemiology, Juno Therapeutics, Finch Therapeutics, Universidad de Costa Rica
Authors: Laustsen, A. H. (Intern), Engmark, M. (Intern), Clouser, C. (Ekstern), Timberlake, S. (Ekstern), Vigneault, F. (Ekstern), Gutiérrez, J. M. (Ekstern), Lomonte, B. (Ekstern)
Number of pages: 18
Publication date: 2017
Main Research Area: Technical/natural sciences

**Publication information**
Journal: PeerJ
Volume: 5
Article number: e2924
ISSN (Print): 2167-8359
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.896 SJR 1.087
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): SJR 1.124 SNIP 0.859 CiteScore 2.36
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.152 SNIP 0.979 CiteScore 2.1
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.998 SNIP 0.84 CiteScore 2.14
Ex vivo back-translation of fostamatinib's effect on joint ECM turnover shows significant effect on bone but no effect on the synovium

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Gentofte University Hospital, Nordic Bioscience A/S
Authors: Kjelgaard-Petersen, C. F. (Intern), Christensen, T. G. (Ekstern), Hagglund, P. (Intern), Karsdal, M. A. (Ekstern), Thudium, C. S. (Ekstern), Bay-Jensen, A. (Ekstern)
Number of pages: 2
Pages: 1068-1069
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Annals of the Rheumatic Diseases
Volume: 76
Article number: AB0062
ISSN (Print): 0003-4967
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 8.02 SJR 7.083 SNIP 3.603
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.909 SNIP 3.255 CiteScore 7.4
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.505 SNIP 2.887 CiteScore 6.78
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.166 SNIP 2.889 CiteScore 7.28
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 5.031 SNIP 3.114 CiteScore 7.79
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 4.637 SNIP 2.741 CiteScore 7.16
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.859 SNIP 2.507
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.226 SNIP 2.196
Fatty acid composition and phospholipid types used in infant formulas modifies the establishment of human gut bacteria in germ-free mice

Human milk fat contains high concentrations of medium-chained fatty acids (MCFA) and triacylglycerols emulsified by a sphingomyelin-rich phospholipid membrane (milk phospholipids, MPL). Infant formula comprises mainly long-chained fatty acids (LCFA) emulsified with dairy proteins and soy lecithin (SL) lacking sphingomyelin. Sphingomyelin content and saturation level of phospholipids affect the gut lipase activity, which alters the concentrations of lipid hydrolysis products in ileum and colon, and hereby putatively affects the competitive advantage of specific gut bacteria. Thus, differences in phospholipid and FA composition may modulate the establishment of the gut microbiota. We investigated effects of fatty acid (FA) composition and emulsification (MPL vs SL) ingested during establishment of human gut microbiota in germ-free mice, and found that cecal microbiotas from mice given MCFA-rich emulsions were characterized by high relative abundances of Bacteroidaceae and Desulfovibrionaceae, while LCFA-rich emulsions caused higher abundances of Enterobacteriaceae, Erysipelotrichaceae, Coriobacteriaceae and Enterococcaceae. Consumption of SL-emulsified lipids skewed the community towards more Enterococcaceae and Enterobacteriaceae, while MPL increased Bacteroidaceae, Rikkennellaceae and Porphyromonadaceae. Intake of SL increased cecal concentrations of isovaleric and iso-butyric acids. This suggests that fat-type and emulsifiers applied in infant formula may have distinct effects on the establishment of the gut microbiota in formula-fed infants.

General information
State: Published
Organisations: National Food Institute, Department of Systems Biology, Copenhagen Center for Health Technology, Research Group for Gut Microbiology and Immunology, Department of Biotechnology and Biomedicine, Systems Metabolic Lipidology
Authors: Bennike, R. M. G. (Intern), Licht, T. R. (Intern), Hellgren, L. (Intern)
Number of pages: 11
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Scientific Reports
Volume: 7
Issue number: 1
Article number: 3975
ISSN (Print): 2045-2322
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 1.245 SJR 1.533
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.63 SJR 1.692 SNIP 1.354
Filling The Gaps In The Kirromycin Biosynthetic Gene Cluster In Streptomyces Collinus Tü 365

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, Department of Biotechnology and Biomedicine, Natural Product Discovery, Eberhard-Karls-Universität Tübingen
Authors: Robertsen, H. L. (Intern), Musiol-Kroll, E. M. (Ekstern), Ding, L. (Intern), Lee, S. Y. (Intern), Weber, T. (Intern)
Publication date: 2017
Event: Abstract from 18th International Symposium on the Biology of Actinomycetes, Jeju, Korea, Republic of.
Main Research Area: Technical/natural sciences
Electronic versions:
170407_ISBA18_Abstract_ver5.pdf
DOIs:
10.1038/s41598-017-04298-0
Source: FindIt
Source-ID: 2371518265
Publication: Research - peer-review › Journal article – Annual report year: 2017

Forskellige virusstammer var årsag til udbrud af plasmacytose i danske mink (Neovison vison) i 2015

General information
State: Published
Organisations: National Veterinary Institute, Virology, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Diagnostic & Development, Department of Biotechnology and Biomedicine, Kopenhagen Fur
Pages: 163-167
Publication date: 2017

Host publication information
Title of host publication: Faglig årsberetning 2016 : Kopenhagen Fur
Place of publication: Aarhus N
Publisher: Kopenhagen Fur
Main Research Area: Technical/natural sciences
Electronic versions:
DTU5.pdf
Publication: Research - peer-review › Book chapter – Annual report year: 2017
From Cell Death to Metabolism: Holin-Antiholin Homologues with New Functions

Programmed cell death in bacteria is generally triggered by membrane proteins with functions analogous to those of bacteriophage holins: they disrupt the membrane potential, whereas antiholins antagonize this process. The holin-like class of proteins is present in all three domains of life, but their functions can be different, depending on the species. Using a series of biochemical and genetic approaches, in a recent article in mBio, Charbonnier et al. (mBio 8:e00976-17, 2017, https://doi.org/10.1128/mBio.00976-17) demonstrate that the antiholin homologue in Bacillus subtilis transports pyruvate and is regulated in an unconventional way by its substrate molecule. Here, we discuss the connection between cell death and metabolism in various bacteria carrying genes encoding these holin-antiholin analogues and place the recent study by Charbonnier et al. in an evolutionary context.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, University of Groningen
Authors: van den Esker, M. H. (Ekstern), Kovács, Á. T. (Intern), Kuipers, O. P. (Ekstern)
Number of pages: 5
Publication date: 2017
Main Research Area: Technical/natural sciences
Publication Information
Journal: mBio (Print)
Volume: 8
Issue number: 6
Article number: e01963-17
ISSN (Print): 2161-2129
Ratings:
Web of Science (2018): Indexed yes
Web of Science (2017): Indexed Yes
Scopus rating (2016): CiteScore 5.79
Scopus rating (2015): CiteScore 4.93
Web of Science (2015): Indexed yes
Scopus rating (2014): CiteScore 4.23
Web of Science (2014): Indexed yes
Scopus rating (2013): CiteScore 4.26
ISI indexed (2013): ISI indexed no
Web of Science (2013): Indexed yes
Scopus rating (2012): CiteScore 4.08
ISI indexed (2012): ISI indexed no
Scopus rating (2011): CiteScore 4.33
ISI indexed (2011): ISI indexed no
Original language: English
Bacillus subtilis, Staphylococcus aureus, Antiholin, Evolution, Holin, Metabolism, Programmed cell death, Pyruvate
Electronic versions:
58_vandenEsker_2017_mBio.pdf
Functional and structural characterization of plastidic starch phosphorylase during barley endosperm development

The production of starch is essential for human nutrition and represents a major metabolic flux in the biosphere. The biosynthesis of starch in storage organs like barley endosperm operates via two main pathways using different substrates: starch synthases use ADP-glucose to produce amylose and amylopectin, the two major components of starch, whereas starch phosphorylase (Pho1) uses glucose-1-phosphate (G1P), a precursor for ADP-glucose production, to produce α-1,4 glucans. The significance of the Pho1 pathway in starch biosynthesis has remained unclear. To elucidate the importance of barley Pho1 (HvPho1) for starch biosynthesis in barley endosperm, we analyzed HvPho1 protein production and enzyme activity levels throughout barley endosperm development and characterized structure-function relationships of HvPho1. The molecular mechanisms underlying the initiation of starch granule biosynthesis, that is, the enzymes and substrates involved in the initial transition from simple sugars to polysaccharides, remain unclear. We found that HvPho1 is present as an active protein at the onset of barley endosperm development. Notably, purified recombinant protein can catalyze the de novo production of α-1,4-glucans using HvPho1 from G1P as the sole substrate. The structural properties of HvPho1 provide insights into the low affinity of HvPho1 for large polysaccharides like starch or amylopectin. Our results suggest that HvPho1 may play a role during the initiation of starch biosynthesis in barley.

General information

State: Published
Organisations: Department of Chemistry, Organic Chemistry, Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Carlsberg Research Laboratory, Virginia Polytechnic Institute and State University
Authors: Cuesta-Seijo, J. A. (Ekstern), Ruzanski, C. (Ekstern), Krucewicz, K. (Ekstern), Meier, S. (Intern), Hägglund, P. (Intern), Svensson, B. (Intern), Palcic, M. M. (Ekstern), Zhang, Y. P. (ed.) (Ekstern)
Number of pages: 25
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information

Journal: P L o S One
Volume: 12
Issue number: 4
Article number: e0175488
ISSN (Print): 1932-6203
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Functional reconstitution of the Trypacidin Gene Cluster in Aspergillus fumigatus by Advanced Gene Editing

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Eukaryotic Molecular Cell Biology, Friedrich-Schiller-Universitat Jena
Authors: Weber, J. (Ekstern), Valiante, V. (Ekstern), Nødvig, C. S. (Intern), Mattern, D. J. (Ekstern), Slotkowski, R. A. (Ekstern), Mortensen, U. H. (Intern), Brakhage, A. A. (Ekstern)
Number of pages: 1
Publication date: 2017
Event: Abstract from 29th Fungal Genetics Conference, Pacific Grove, United States.
Main Research Area: Technical/natural sciences
Electronic versions:
Functional_reconstitution_of_the_Trypacidin_Gene_Cluster_in_Aspergillus.pdf
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

Fungal secretomics to probe the biological functions of lytic polysaccharide monooxygenases

Enzymatic degradation of plant biomass is of growing interest for the development of a sustainable bio-based industry. Filamentous fungi, which degrade complex and recalcitrant plant polymers, are proficient secretors of enzymes acting on the lignocellulose composite of plant cell walls in addition to starch, the main carbon storage reservoir. In this review, we focus on the identification of lytic polysaccharide monooxygenases (LPMOs) and their redox partners in fungal secretomes to highlight the biological functions of these remarkable enzyme systems and we discuss future trends related to LPMO-potentiated bioconversion.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Protein Glycoscience and Biotechnology, Aix-Marseille University
Authors: Berrin, J. (Ekstern), Rosso, M. (Ekstern), Abou Hachem, M. (Intern)
Number of pages: 6
Pages: 155-160
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Carbohydrate Research
Volume: 448
ISSN (Print): 0008-6215

Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.744 SJR 0.617
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.03 SJR 0.659 SNIP 0.796
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.588 SNIP 0.828 CiteScore 1.98
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.64 SNIP 0.85 CiteScore 2.01
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.64 SNIP 0.852 CiteScore 2.22
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.772 SNIP 1.01 CiteScore 2.2
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.762 SNIP 1.058 CiteScore 2.43
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.73 SNIP 0.872
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.888 SNIP 1.024
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.859 SNIP 0.947
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.759 SNIP 0.891
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.643 SNIP 0.903
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.693 SNIP 0.992
Scopus rating (2004): SJR 0.636 SNIP 0.95
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.712 SNIP 0.976
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.77 SNIP 0.948
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.731 SNIP 0.829
Scopus rating (2000): SJR 0.797 SNIP 1
FurIOS: a web-based tool for identification of Vibrionaceae species using the fur gene

Gene based methods for identification of species from the Vibrionaceae family have been developed during the last decades to address the limitations of the commonly used 16S rRNA gene phylogeny. Recently, we found that the ferric-uptake regulator gene (fur) can be used as a single identification marker providing species discrimination, consistent with multi-locus sequencing analyses and whole genome phylogenies. To allow for broader and easy use of this marker, we have developed an online prediction service that allows the identification of Vibrionaceae species based on their fur-sequence. The input is a DNA sequence that can be uploaded on the web service; the output is a table containing the strain identifier, e-value, and percentage of identity for each of the matches with rows colored in green for hits with high probability of being the same species. The service is available on the web at: http://www.cbs.dtu.dk/services/furIOS-1.0/.

The fur-sequences can be derived either from genome sequences or from PCR-amplification of the genomic region encoding the fur gene. We have used 191 strains identified as Vibrionaceae based on 16S rRNA gene sequence to test the PCR method and the web service on a large dataset. We were able to classify 171 of 191 strains at the species level and 20 strains remained unclassified. Furthermore, the fur phylogenetics and subsequent in silico DNA-DNA hybridization demonstrated that two strains (ATCC 33789 and ZS-139) previously identified as Vibrio splendidus are more closely related to V. tasmaniensis and V. cyclitrophicus, respectively. FurIOS is an easy-to-use online service that allows the identification of bacteria from the Vibrionaceae family at the species level using the fur gene as a single marker. Its simplistic design and straightforward pipeline makes it suitable for any research environment, from academia to industry.

Introduction

General information

State: Published
Organisations: Department of Systems Biology, Bacterial Ecophysiology and Biotechnology, Novo Nordisk Foundation Center for Biosustainability, iLoop, Center for Biological Sequence Analysis, Department of Bio and Health Informatics, Genomic Epidemiology, Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology
Authors: Machado, H. (Intern), Cardoso, J. (Intern), Giubergia, S. (Intern), Rapacki, K. (Intern), Gram, L. (Intern)
Number of pages: 8
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information

Journal: BMC Microbiology
Volume: 8
Article number: 414
ISSN (Print): 1471-2180
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SNIP 0.953 SJR 1.242
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.82 SJR 1.282 SNIP 0.993
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.42 SNIP 0.994 CiteScore 2.93
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.519 SNIP 1.069 CiteScore 2.95
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.571 SNIP 1.179 CiteScore 3.32
Gene expression plasticity across hosts of an invasive scale insect species
For plant-eating insects, we still have only a nascent understanding of the genetic basis of host-use promiscuity. Here, to improve that situation, we investigated host-induced gene expression plasticity in the invasive lobate lac scale insect, Paratachardina pseudolobata (Hemiptera: Keridae). We were particularly interested in the differential expression of detoxification and effector genes, which are thought to be critical for overcoming a plant’s chemical defenses. We collected RNA samples from P. pseudolobata on three different host plant species, assembled transcriptomes de novo, and identified transcripts with significant host-induced gene expression changes. Gene expression plasticity was pervasive, but the expression of most detoxification and effector genes was insensitive to the host environment. Nevertheless, some types of detoxification genes were more differentially expressed than expected by chance. Moreover, we found evidence of a trade-off between expression of genes involved in primary and secondary metabolism; hosts that induced lower expression of genes for detoxification induced higher expression of genes for growth. Our findings are largely consonant with those of several recently published studies of other plant-eating insect species. Thus, across plant-
eating insect species, there may be a common set of gene expression changes that enable host-use promiscuity.

**General information**

State: Published
Organisations: Department of Systems Biology, Eucaryotic Molecular Cell Biology, Department of Biotechnology and Biomedicine, Biosynthetic Pathway Engineering, Eukaryotic Molecular Cell Biology, Department of Bio and Health Informatics, Metagenomics, Auburn University, University of Massachusetts
Authors: Christodoulides, N. (Ekstern), Van Dam, A. (Intern), Peterson, D. A. (Ekstern), Frandsen, R. J. N. (Intern), Mortensen, U. H. (Intern), Petersen, B. (Intern), Rasmussen, S. (Intern), Normark, B. B. (Ekstern), Hardy, N. B. (Ekstern)
Number of pages: 13
Publication date: 2017
Main Research Area: Technical/natural sciences

**Publication information**

Journal: P L o S One
Volume: 12
Issue number: 5
Article number: e0176956
ISSN (Print): 1932-6203
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.425 SNIP 1.233 CiteScore 4.58
ISI indexed (2011): ISI indexed no
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.705 SNIP 1.178
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.614 SNIP 1.046
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.506 SNIP 1.006
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.379 SNIP 0.537
Web of Science (2006): Indexed yes
Gene expression profiling in persons with multiple chemical sensitivity before and after a controlled n-butanol exposure session

To investigate the pathophysiological pathways leading to symptoms elicitation in multiple chemical sensitivity (MCS) by comparing gene expression in MCS participants and healthy controls before and after a chemical exposure optimised to cause symptoms among MCS participants. The first hypothesis was that unexposed and symptom-free MCS participants have similar gene expression patterns to controls and a second hypothesis that MCS participants can be separated from controls based on differential gene expression upon a controlled n-butanol exposure. Participants were exposed to 3.7 ppm n-butanol while seated in a windowed exposure chamber for 60 min. A total of 26 genes involved in biochemical pathways found in the literature have been proposed to play a role in the pathogenesis of MCS and other functional somatic syndromes were selected. Expression levels were compared between MCS and controls before, within 15 min after being exposed to and 4 hours after the exposure. Participants suffering from MCS and healthy controls were recruited through advertisement at public places and in a local newspaper. 36 participants who considered themselves sensitive were prescreened for eligibility. 18 sensitive persons fulfilling the criteria for MCS were enrolled together with 18 healthy controls. 17 genes showed sufficient transcriptional level for analysis. Group comparisons were conducted for each gene at the 3 time points and for the computed area under the curve (AUC) expression levels. MCS participants and controls displayed similar gene expression levels both at baseline and after the exposure and the computed AUC values were likewise comparable between the 2 groups. The intragroup variation in expression levels among MCS participants was noticeably greater than the controls. MCS participants and controls have similar gene expression levels at baseline and it was not possible to separate MCS participants from controls based on gene expression measured after the exposure.

General information
State: Published
Organisations: Department of Systems Biology, Department of Biotechnology and Biomedicine, Systems Metabolic Lipidology, Research Centre for Prevention and Health, Umeå University, Copenhagen University Hospital, Swedish University of Agricultural Sciences
Authors: Dantoft, T. M. (Intern), Skovbjerg, S. (Ekstern), Andersson, L. (Ekstern), Claeson, A. (Ekstern), Engkilde, K. (Ekstern), Lind, N. (Ekstern), Nordin, S. (Ekstern), Hellgren, L. (Intern)
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Web of Science (2018): Indexed yes
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Web of Science (2017): Indexed yes
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BFI (2015): BFI-level 1
BFI (2014): BFI-level 1
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
ISI indexed (2013): ISI indexed no
BFI (2012): BFI-level 1
ISI indexed (2012): ISI indexed no
Original language: English
Chemical exposure, Exposure chamber, Gene expression, Multiple Chemical Sensitivity, qPCR
Genes Linked to Production of Secondary Metabolites in Talaromyces atroroseus Revealed Using CRISPR-Cas9

The full potential of fungal secondary metabolism has until recently been impeded by the lack of universal genetic tools for most species. However, the emergence of several CRISPR-Cas9-based genome editing systems adapted for several genera of filamentous fungi have now opened the doors for future efforts in discovery of novel natural products and elucidation and engineering of their biosynthetic pathways in fungi where no genetic tools are in place. So far, most studies have focused on demonstrating the performance of CRISPR-Cas9 in various fungal model species, and recently we presented a versatile CRISPR-Cas9 system that can be successfully applied in several diverse Aspergillus species. Here we take it one step further and show that our system can be used also in a phylogenetically distinct and largely unexplored species from the genus of Talaromyces. Specifically, we exploit CRISPR-Cas9-based genome editing to identify a new gene in T. atroroseus responsible for production of polyketide-nonribosomal peptide hybrid products, hence, linking fungal secondary metabolites to their genetic origin in a species where no genetic engineering has previously been performed.

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Main Research Area: Technical/natural sciences

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Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.427 SNIP 1.136 CiteScore 3.32
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.559 SNIP 1.148 CiteScore 3.54
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.772 SNIP 1.153 CiteScore 3.94
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 1.982 SNIP 1.156 CiteScore 4.15
ISI indexed (2012): ISI indexed yes
Genetic diversity of 100+ Aspergillus species - the aspMine analysis resource

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, CBS-KNAW Fungal Biodiversity Centre, Joint Bioenergy Institute, Joint Genome Institute
Authors: Vesth, T. C. (Intern), Rasmussen, J. L. N. (Intern), Theobald, S. (Intern), De Vries, R. (Ekstern), Grigoriev, I. V. (Ekstern), Baker, S. E. (Ekstern), Andersen, M. R. (Intern)
Number of pages: 1
Publication date: 2017
Event: Abstract from 29th Fungal Genetics Conference, Pacific Grove, United States.
Main Research Area: Technical/natural sciences
Electronic versions:
Genetic_diversity_of_100_Aspergillus_species_the_aspMine_analysis_resource..pdf
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

Genome Sequence of Talaromyces atroroseus, Which Produces Red Colorants for the Food Industry
Talaromyces atroroseus is a known producer of Monascus colorants suitable for the food industry. Furthermore, genetic tools have been established that facilitate elucidation and engineering of its biosynthetic pathways. Here, we report the draft genome of a potential fungal cell factory, T. atroroseus IBT 11181 (CBS 123796).

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Department of Systems Biology, Department of Bio and Health Informatics, Metagenomics, Metagenomics, Eukaryotic Molecular Cell Biology
Authors: Thrane, U. (Intern), Rasmussen, K. B. (Intern), Petersen, B. (Intern), Rasmussen, S. (Intern), Sicheritz-Pontén, T. (Intern), Mortensen, U. H. (Intern)
Number of pages: 2
Publication date: 2017
Main Research Area: Technical/natural sciences

Publication information
Journal: Genome Announcements
Volume: 5
Genome-wide analyses of Listeria monocytogenes from food-processing plants reveals clonal diversity and dates the emergence of persisting sequence types

Whole genome sequencing is increasing used in epidemiology, e.g. for tracing outbreaks of food-borne diseases. This requires in-depth understanding of pathogen emergence, persistence, and genomic diversity along the food production chain including in food processing plants. We sequenced the genomes of 80 isolates of Listeria monocytogenes sampled from Danish food processing plants over a time-period of 20 years, and analyzed the sequences together with 10 public available reference genomes to advance our understanding of inter- and intra-plant genomic diversity of L. monocytogenes. Except for three persisting sequence types (ST) based on Multi Locus Sequence Typing (MLST) being ST7, ST8 and ST121, long-term persistence of clonal groups was limited, and new clones were introduced continuously, potentially from raw materials. No particular gene could be linked to the persistence phenotype. Using time-based phylogenetic analyses of the persistent STs, we estimate the L. monocytogenes evolutionary rate to be 0.18-0.35 SNPs/year, suggesting that the persistent STs emerged approximately 100 years ago, which correlates with the onset of industrialization and globalization of the food market.
Genomic Diversity in the Genus of Aspergillus

Aspergillus is a highly important genus of saprotrophic filamentous fungi. It is a very diverse genus that is inextricably intertwined with human affairs on a daily basis, holding species relevant to plant and human pathology, enzyme and bulk chemistry production, food and beverage biotechnology, and scientific model organisms. The phenotypic diversity in this genus is extraordinary and identifying the genetic basis for this diversity has great potential for academia and industry. When the genomic era began for Aspergillus in 2005 with the genome sequences of A. nidulans, A. oryzae and A. fumigatus, it was quickly apparent that a large part of understanding the individual species and genetic features comes from performing comparative genomics. This is what the Aspergillus whole-genus sequencing project will facilitate, which aim to sequence and study the genomes of all 350 members in genus Aspergillus. This thesis has utilized this resource to study the genome diversity in the Aspergillus genus, with a focus on how the genetic variation affects speciation. In the work presented here, a new homolog identification tool has been developed based on BLAST alignments of protein sequences and single linkage. The advantage of this tool is its ability to link homologs with diverse evolutionary histories, thus accommodating the genetic variances that has accumulated over > 200 million years in genus Aspergillus.

Throughout this work, HomologSL has been used to investigate genome diversity within species, clades, sections and genus of Aspergillus. The work uncovers a large genomic diversity across all studied groups of species. The genomic diversity was especially evident on the section level, where the proteins shared by all species only represents ~155% of the proteome. This number decreases even further, to 38%, for protein shared by the whole genus. The work further identifies the species-unique genes holding a large unexplored potential of both enzymes and secondary metabolites. Through the analysis of the shared and species-unique genes, this study presents genes and functions that defines genus Aspergillus, sections Nigri, Usti and Cavericolus, clade Tubingensis, and species A. niger. It lastly uses these results to predict genetic traits that take part in fungal speciation. Within a few years the Aspergillus whole-genus sequencing project will have published all currently-accepted Aspergillus genomes, providing the Aspergillus community with a resource that will allow for research within comparative genomics, which has not been possible in any fungal genera before. The work presented here is part of this project, releasing both comparative genomics tools and > 40 genomes to make it happen.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Rasmussen, J. L. N. (Intern), Andersen, M. R. (Intern), Vesth, T. C. (Intern)
Number of pages: 9
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Publication information
Publisher: Technical University of Denmark (DTU)
Original language: English
Main Research Area: Technical/natural sciences
Genomic epidemiology of a major Mycobacterium tuberculosis outbreak: Retrospective cohort study in a low incidence setting using sparse time-series sampling

Since 1992, Denmark has documented the largest outbreak of tuberculosis in Scandinavia ascribed to a single genotype, termed 'C2/1112-15'. As of spring 2017, the International Reference Laboratory of Mycobacteriology in Copenhagen has collected and identified isolates from more than a thousand cases belonging to this outbreak via routine MIRU-VNTR typing. Here, we present a retrospective analysis of the C2/1112-15 dataset, based on whole-genome data from a sparse time-series consisting of five randomly selected isolates from each of the 23 years. Even if these data are derived from only 12% of the collected isolates, we have been able to extract important key information, such as mutation rate, conserved single-nucleotide polymorphisms to identify discrete transmission chains, as well as the possible historical origins of the outbreak.
Genomic GC-content affects the accuracy of 16S rRNA gene sequencing based microbial profiling due to PCR bias

Profiling of microbial community composition is frequently performed by partial 16S rRNA gene sequencing on benchtop platforms following PCR amplification of specific hypervariable regions within this gene. Accuracy and reproducibility of this strategy are two key parameters to consider, which may be influenced during all processes from sample collection and storage, through DNA extraction and PCR based library preparation to the final sequencing. In order to evaluate both the reproducibility and accuracy of 16S rRNA gene based microbial profiling using the Ion Torrent PGM platform, we prepared libraries and performed sequencing of a well-defined and validated 20-member bacterial DNA mock community on five separate occasions and compared results with the expected even distribution. In general the applied method had a median coefficient of variance of 11.8% (range 5.5-73.7%) for all 20 included strains in the mock community across five separate sequencing runs, with underrepresented strains generally showing the largest degree of variation. In terms of accuracy, mock community species belonging to Proteobacteria were underestimated, whereas those belonging to Firmicutes were mostly overestimated. This could be explained partly by premature read truncation, but to larger degree their genomic GC-content, which correlated negatively with the observed relative abundances, suggesting a PCR bias against GC-rich species during library preparation. Increasing the initial denaturation time during the PCR amplification from 30 to 120 s resulted in an increased average relative abundance of the three mock community members with the highest genomic GC%, but did not significantly change the overall evenness of the community distribution. Therefore, efforts should be made to optimize the PCR conditions prior to sequencing in order to maximize accuracy.

General Information
State: Published
Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Bio and Health Informatics, DTU Multi Assay Core
Authors: Laursen, M. F. (Intern), Dalgaard, M. D. (Intern), Bahl, M. I. (Intern)
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Genus level analysis of secondary metabolism reveals the origin of Aspergillus hybrid NRPS-PKS gene clusters

General information
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Organisations: Department of Biotechnology and Biomedicine, Novo Nordisk Foundation Center for Biosustainability, Network Engineering of Eukaryotic Cell factories, New Bioactive Compounds, Fungal Chemodiversity, Natural Product Discovery, Eukaryotic Molecular Cell Biology, Joint Genome Institute, Joint Bioenergy Institute
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Main Research Area: Technical/natural sciences
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Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

GH62 arabinofuranosidases: Structure, function and applications
Motivated by industrial demands and ongoing scientific discoveries continuous efforts are made to identify and create improved biocatalysts dedicated to plant biomass conversion. α-1,2 and α-1,3 arabinofuranosyl specific α-l-arabinofuranosidases (EC 3.2.1.55) are debranching enzymes catalyzing hydrolytic release of α-l-arabinofuranosyl residues, which decorate xylan or arabinan backbones in lignocellulosic and pectin constituents of plant cell walls. The CAZy database classifies α-l-arabinofuranosidases in Glycoside Hydrolase (GH) families GH2, GH3, GH43, GH51, GH54 and GH62. Only GH62 contains exclusively α-l-arabinofuranosidases and these are of fungal and bacterial origin. Twenty-two GH62 enzymes out of 223 entries in the CAZy database have been characterized and very recently new knowledge was acquired with regard to crystal structures, substrate specificities, and phylogenetics, which overall provides novel insights into structure/function relationships of GH62. Overall GH62 α-l-arabinofuranosidases are believed to play important roles in nature by acting in synergy with several cell wall degrading enzymes and members of GH62 represent...
promising candidates for biotechnological improvements of biofuel production and in various biorefinery applications.
Global analysis of biosynthetic gene clusters reveals vast potential of secondary metabolite production in Penicillium species

Filamentous fungi produce a wide range of bioactive compounds with important pharmaceutical applications, such as antibiotic penicillins and cholesterol-lowering statins. However, less attention has been paid to fungal secondary metabolites compared to those from bacteria. In this study, we sequenced the genomes of 9 Penicillium species and, together with 15 published genomes, we investigated the secondary metabolism of Penicillium and identified an immense, unexploited potential for producing secondary metabolites by this genus. A total of 1,317 putative biosynthetic gene clusters (BGCs) were identified, and polyketide synthase and non-ribosomal peptide synthetase based BGCs were grouped into gene cluster families and mapped to known pathways. The grouping of BGCs allowed us to study the evolutionary trajectory of pathways based on 6-methylsalicylic acid (6-MSA) synthases. Finally, we cross-referenced the predicted pathways with published data on the production of secondary metabolites and experimentally validated the production of antibiotic yanuthones in Penicillia and identified a previously undescribed compound from the yanuthone pathway. This study is the first genus-wide analysis of the genomic diversity of Penicillia and highlights the potential of these species as a source of new antibiotics and other pharmaceuticals.

Global gruppering af plasmacytosevirus isoleret fra mink (Neovison vison)
Global transcriptional response of solvent-sensitive and solvent-tolerant Pseudomonas putida strains exposed to toluene

*Pseudomonas putida* strains are generally recognized as solvent tolerant, exhibiting varied sensitivity to organic solvents. Pan-genome analysis has revealed that 30% of genes belong to the core-genome of *Pseudomonas*. Accessory and unique genes confer high degree of adaptability and capabilities for the degradation and synthesis of a wide range of chemicals. For the use of these microbes in bioremediation and biocatalysis, it is critical to understand the mechanisms underlying these phenotypic differences. In this study, RNA-seq analysis compared the short- and long-term responses of the toluene-sensitive KT2440 strain and the highly-tolerant DOT-T1E strain. The sensitive strain activates a larger number of genes in a higher magnitude than DOT-T1E. This is expected because KT2440 bears one toluene tolerant pump, while DOT-T1E encodes three of these pumps. Both strains activate membrane modifications to reduce toluene membrane permeability. The KT2440 strain activates the TCA cycle to generate energy, while avoiding energy-intensive processes such as flagellar biosynthesis. This suggests that KT2440 responds to toluene by focusing on survival mechanisms. The DOT-T1E strain activates toluene degradation pathways, using toluene as source of energy. Among the unique genes encoded by DOT-T1E is a 70kb island composed of genes of unknown function induced in response to toluene.
Growth on Chitin Impacts the Transcriptome and Metabolite Profiles of Antibiotic-Producing Vibrio coralliilyticus S2052 and Photobacterium galatheae S2753

Members of the Vibrionaceae family are often associated with chitin-containing organisms, and they are thought to play a major role in chitin degradation. The purpose of the present study was to determine how chitin affects the transcriptome and metabolome of two bioactive Vibrionaceae strains, Vibrio coralliilyticus and Photobacterium galatheae. We focused on chitin degradation genes and secondary metabolites based on the assumption that these molecules in nature confer an advantage to the producer. Growth on chitin caused upregulation of genes related to chitin metabolism and of genes potentially involved in host colonization and/or infection. The expression of genes involved in secondary metabolism was also significantly affected by growth on chitin, in one case being 34-fold upregulated. This was reflected in the metabolome, where the antibiotics andrimid and holomycin were produced in larger amounts on chitin. Other polyketide synthase/ nonribosomal peptide synthetase (PKS-NRPS) clusters in P. galatheae were also strongly upregulated on chitin. Collectively, this suggests that both V. coralliilyticus and P. galatheae have a specific lifestyle for growth on chitin and that their secondary metabolites likely play a crucial role during chitin colonization. IMPORTANCE The bacterial family Vibrionaceae (vibrios) is considered a major player in the degradation of chitin, the most abundant polymer in the marine environment; however, the majority of studies on the topic have focused on a small number of Vibrio species. In this study, we analyzed the genomes of two vibrios to assess their genetic potential for the degradation of chitin. We then used transcriptomics and metabolomics to demonstrate that chitin strongly affects these vibrios at both the transcriptional and metabolic levels. We observed a strong increase in production of secondary metabolites, suggesting an ecological role for...
these molecules during chitin colonization in the marine environment.

**Guiding recombinant antivenom development by omics technologies**

In this review, the different approaches that have been employed with the aim of developing novel antivenoms against animal envenomings are presented and discussed. Reported efforts have focused on the use of innovative immunization strategies, small molecule inhibitors against enzymatic toxins, endogenous animal proteins with toxin-neutralizing capabilities, and recombinant monoclonal antibodies. Harnessing either of these approaches, antivenom development may benefit from an in-depth understanding of venom compositions and the medical importance of individual venom toxins. Focus is thus also directed towards the different omics technologies (particularly venomics, antivenomics, and toxicovenomics) that are being used to uncover novel animal toxins, shed light on venom complexity, and provide directions for how to determine the medical relevance of individual toxins within whole venoms. Finally, techniques for assessing antivenom specificity and cross-reactivity are reviewed, with special focus on antivenomics and high-density peptide microarray technology.
Harnessing off-target effects

The ‘off-targets’ of a drug are often poorly characterized yet could be harnessed in the treatment of complex diseases. A recent study used a small-molecule screening in non-small-cell lung cancer to repurpose an FDA-approved ALK/IGF1R inhibitor and uncover its mechanism of action.

General information
State: Published
Hierarchical Sets: Analyzing Pangenome Structure through Scalable Set Visualizations

The increase in available microbial genome sequences has resulted in an increase in the size of the pangenomes being analyzed. Current pangenome visualizations are not intended for the pangenome sizes possible today and new
approaches are necessary in order to convert the increase in available information to increase in knowledge. As the pangenome data structure is essentially a collection of sets we explore the potential for scalable set visualization as a tool for pangenome analysis. We present a new hierarchical clustering algorithm based on set arithmetics that optimizes the intersection sizes along the branches. The intersection and union sizes along the hierarchy are visualized using a composite dendrogram and icicle plot, which, in pangenome context, shows the evolution of pangenome and core size along the evolutionary hierarchy. Outlying elements, i.e. elements whose presence pattern do not correspond with the hierarchy, can be visualized using hierarchical edge bundles. When applied to pangenome data this plot shows putative horizontal gene transfers between the genomes and can highlight relationships between genomes that is not represented by the hierarchy. We illustrate the utility of hierarchical sets by applying it to a pangenome based on 113 Escherichia and Shigella genomes and find it provides a powerful addition to pangenome analysis. The described clustering algorithm and visualizations are implemented in the hierarchicalSets R package available from CRAN (https://cran.r-project.org/web/packages/hierarchicalSets) CONTACT: Thomas Lin Pedersen (thomasp85@gmail.com)Supplementary information Supplementary data are available at Bioinformatics online.

General information
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Organisations: Center for Biological Sequence Analysis, Department of Biotechnology and Biomedicine
Authors: Pedersen, T. L. (Intern)
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BFI (2017): BFI-level 2
Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Indexed yes
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Scopus rating (2015): CiteScore 6.06
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BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.5
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Scopus rating (2013): CiteScore 5.78
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Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 6.73
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 5.61
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
High-density peptide microarray exploration of the antibody response in a rabbit immunized with a neurotoxic venom fraction

Polyvalent snakebite antivenoms derive their therapeutic success from the ability of their antibodies to neutralize venom toxins across multiple snake species. This ability results from a production process involving immunization of large mammals with a broad suite of toxins present in venoms. As a result of immunization with this wide range of toxins, many polyvalent antivenoms have a high degree of cross-reactivity to similar toxins in other snake venoms - a cross-reactivity which cannot easily be deconvoluted. As a proof of concept, we aimed at exploring the opposite scenario by performing a high-throughput evaluation of the extent of cross-reactivity of a polyclonal mixture of antibodies that was raised against only a single snake venom fraction. For this purpose, a venom fraction containing short neurotoxin 1 (SN-1, Uniprot accession number P01416, three-finger toxin (3FTx) family), which is the medically most important toxin from the notorious black mamba (Dendroaspis polylepis), was employed. Following immunization of a rabbit, a specific polyclonal antibody response was confirmed by ELISA and immunodiffusion. Subsequently, these antibodies were investigated by high-density peptide microarray to reveal linear elements of recognized epitopes across 742 3FTxs and 10 dendrotoxins. This exploratory study demonstrates in a single immunized animal that cross-reactivity between toxins of high similarity may be difficult to obtain when immunizing with a single 3FTx containing venom fraction. Additionally, this study explored the influence of employing different lengths of peptides in high-density peptide microarray experiments for identification of toxin epitopes. Using 8-mer, 12-mer, and 15-mer peptides, a single linear epitope element was identified in SN-1 with high precision.
Dendroaspis polylepis, Epitope mapping, Short neurotoxin, Single toxin immunization, Three-finger toxin

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High throughput resistance profiling of Plasmodium falciparum infections based on custom dual indexing and Illumina next generation sequencing-technology

Genetic polymorphisms in P. falciparum can be used to indicate the parasite's susceptibility to antimalarial drugs as well as its geographical origin. Both of these factors are key to monitoring development and spread of antimalarial drug resistance. In this study, we combine multiplex PCR, custom designed dual indexing and MiSeq sequencing for high throughput SNP-profiling of 457 malaria infections from Guinea-Bissau, at the cost of 10 USD per sample. By amplifying and sequencing 15 genetic fragments, we cover 20 resistance-conferring SNPs occurring in pfcrt, pfmdr1, pfdfhr, pfhpfs, as well as the entire length of pfK13, and the mitochondrial barcode for parasite origin. SNPs of interest were sequenced with an average depth of 2,043 reads, and bases were called for the various SNP-positions with a p-value below 0.05, for 89.8-100% of samples. The SNP data indicates that artemisinin resistance-conferring SNPs in pfK13 are absent from the studied area of Guinea-Bissau, while the pfmdr1 86 N allele is found at a high prevalence. The mitochondrial barcodes are unanimous and accommodate a West African origin of the parasites. With this method, very reliable high throughput surveillance of antimalarial drug resistance becomes more affordable than ever before.
HPLC-HRMS Quantification of the Ichthyotoxin Karmitoxin from Karlodinium armiger

Being able to quantify ichthyotoxic metabolites from microalgae allows for the determination of ecologically-relevant concentrations that can be simulated in laboratory experiments, as well as to investigate bioaccumulation and degradation. Here, the ichthyotoxin karmitoxin, produced by Karlodinium armiger, was quantified in laboratory-grown cultures using high-performance liquid chromatography (HPLC) coupled to electrospray ionisation high-resolution time-of-flight mass spectrometry (HRMS). Prior to the quantification of karmitoxin, a standard of karmitoxin was purified from K. armiger cultures (80 L). The standard was quantified by fluorescent derivatisation using Waters AccQ-Fluor reagent and derivatised fumonisin B₁ and fumonisin B₂ as standards, as each contain a primary amine. Various sample preparation methods for whole culture samples were assessed, including six different solid phase extraction substrates. During analysis of culture samples, MS source conditions were monitored with chloramphenicol and valinomycin as external
standards over prolonged injection sequences (>12 h) and karmitoxin concentrations were determined using the response factor of a closely eluting iturin A2 internal standard. Using this method the limit of quantification was 0.11 μg·mL⁻¹, and the limit of detection was found to be 0.03 μg·mL⁻¹. Matrix effects were determined with the use of K. armiger cultures grown with 13C-labelled bicarbonate as the primary carbon source.

**General information**

State: Published
Organisations: National Food Institute, Department of Biotechnology and Biomedicine, Natural Product Discovery, DTU Metabolomics Core, Research Group for Analytical Food Chemistry, Universidade Federal de Sao Paulo, University of Copenhagen

Authors: Andersen, A. J. C. (Intern), Soman De Medeiros, L. (Ekstern), Binzer, S. B. (Ekstern), Rasmussen, S. A. (Intern), Hansen, P. J. (Ekstern), Nielsen, K. F. (Intern), Jørgensen, K. (Intern), Larsen, T. O. (Intern)

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Aspergillus labruscus sp. nov., a new species of Aspergillus section Nigri discovered in Brazil

A novel fungal species, Aspergillus labruscus sp. nov., has been found in Brazil during an investigation of the fungal species present on the surface of grape berries (Vitis labrusca L.) for use in the production of concentrated grape juice. It seems to be associated to V. labrusca, and has never been recovered from Vitis vinifera. This new species belonging to Aspergillus subgenus Circumdati section Nigri is described here using morphological characters, extrolite profiling, partial sequence data from the BenA and CaM genes, and internal transcribed spacer sequences of ribosomal DNA. Phenotypic and molecular data enabled this novel species to be clearly distinguished from other black aspergilli. A. labruscus sp. nov. is uniseriate, has yellow mycelium, poor sporulation on CYA at 25°C, abundant salmon to pink sclerotia and rough conidia. Neoxaline and secalonic acid D were consistently produced by isolates in this taxon. The type strain of A. labruscus sp. nov. is CCT 7800 (T) = ITAL 22.223 (T) = IBT 33586 (T).

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Identification of citrullination sites specific for peptidylarginine deiminase 2 (PAD2) and PAD4 in fibrinogen from synovial fluid of patients with rheumatoid arthritis

Background Protein citrullination, i.e. conversion of arginine residues into citrulline residues, is a post-translational modification catalyzed by PAD, and is an important pathophysiological determinant in conditions such as Rheumatoid arthritis (RA). Identification of citrullination sites on putative autoantigens is likely to enhance our understanding of PAD's substrate specificity. Objectives Citrullinated fibrinogen is an autoantigen linked to the pathophysiology of RA. We have applied a novel MS-based proteomics approach to estimate the degree of citrullination in synovial fluid (SF) from RA patients, and compare to fibrinogen citrullinated in vitro by PAD2/4, the most important PAD isoforms involved in RA. The estimated degree of citrullination induced by the two isoforms is also compared to evaluate their relative impact. Methods Fibrinogen was citrullinated in vitro by PAD2/4 and citrullination sites were identified by LC-MS/MS on a Q-exactive orbitrap following proteolytic digestion with Lys-C. These in vitro citrullination profiles were compared to those observed in SF fibrinogen of four RA patients with varying DAS28 scores, CRP levels and leukocyte counts. DAS28 scores >5.1 and ≤ 2.4 correspond to moderate to severe and low activity of disease respectively. Patients with high inflammatory activity gave high CRP level and leukocyte count values. Results A total of 52 citrullination sites were identified. Overall, PAD2 generated higher number of identified sites and higher degree of citrulline occupancy at given sites than PAD4. In fibrinogen from SF, 38 citrullination sites were identified, of which 23 have not been previously reported. Several of these sites were identified in more than one patient, and were regarded as hotspots. Fibrinogen from patients with high DAS28 levels contained markedly more citrullination sites and higher citrulline occupancy. Conclusions Study suggests that PAD2 citrullinates fibrinogen more efficiently than PAD4 and citrullination of certain sites in fibrinogen from SF reflects disease activity. Identification of such sites may have diagnostic or prognostic value in RA and other inflammatory disorders.
Identifying low density lipoprotein cholesterol associated variants in the Annexin A2 (ANXA2) gene

Background and aims: Annexin-A2 (AnxA2) is an endogenous inhibitor of proprotein convertase subtilisin/kexin type-9 (PCSK9). The repeat-one (R1) domain of AnxA2 binds to PCSK9, blocking its ability to promote degradation of low-density lipoprotein cholesterol-receptors (LDL-R) and thereby regulate low-density lipoprotein cholesterol (LDL-C) levels. Here we identify variants in ANXA2 influencing LDL-C levels and we determine the molecular mechanisms of their effects.

Results: The ANXA2 single nucleotide polymorphism (SNP) genotype-phenotype association was examined using the Second-Northwick-Park Heart Study (NPHSII) (n similar to 2700) and the UCL-LSHTM-EdinburghBristol (UCLEB) consortium (n similar to 14,600). The ANXA2-R1 domain coding-SNP rs17845226 (V98L) associated with LDL-C, homozygotes for the minor allele having approximate to 18.8% higher levels of LDL-C (p = 0.004), and higher risk of coronary heart disease (CHD) (p = 0.04). The SNP is in modest linkage disequilibrium (r(2) > 0.5) with two intergenic SNPs, rs17191344 and rs11633032. Both SNPs showed allele-specific protein binding, and the minor alleles caused significant reduction in reporter gene expression (approximate to 18%, p <0.001). In the expression quantitative trait loci (eQTL) study, minor allele homozygotes have significantly lower levels of ANXA2-mRNA expression (p = 1.36 x 10(-05)).

Conclusions: Both rs11633032 and rs17191344 SNPs are functional variants, where the minor alleles create repressor-binding protein sites for transcription factors that contribute to reduced ANXA2 gene expression. Lower AnxA2 levels could increase plasma levels of PCSK9 and thus increase LDL-C levels and risk of CHD. This supports, for the first time in humans, previous observations in mouse models that changes in the levels of AnxA2 directly influence plasma LDL-C levels, and thus implicate this protein as a potential therapeutic target for LDL-C lowering. (C) 2017 The Authors. Published by Elsevier Ireland Ltd.
Identifying more than 300 Biosynthetic Gene Clusters with Potential Resistance Genes in over 75 Aspergillus species using Resistance Gene-Guided Genome Mining

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Industrial antifoam agents impair ethanol fermentation and induce stress responses in yeast cells

The Brazilian sugarcane industry constitutes one of the biggest and most efficient ethanol production processes in the world. Brazilian ethanol production utilizes a unique process, which includes cell recycling, acid wash, and non-aseptic conditions. Process characteristics, such as extensive CO2 generation, poor quality of raw materials, and frequent contaminations, all lead to excessive foam formation during fermentations, which is treated with antifoam agents (AFA). In this study, we have investigated the impact of industrial AFA treatments on the physiology and transcriptome of the industrial ethanol strain Saccharomyces cerevisiae CAT-1. The investigated AFA included industrially used AFA acquired from Brazilian ethanol plants and commercially available AFA commonly used in the fermentation literature. In batch fermentations, it was shown that industrial AFA compromised growth rates and glucose uptake rates, while commercial AFA had no effect in concentrations relevant for defoaming purposes. Industrial AFA were further tested in laboratory scale simulations of the Brazilian ethanol production process and proved to decrease cell viability compared to the control, and the effects were intensified with increasing AFA concentrations and exposure time. Transcriptome analysis showed that AFA treatments induced additional stress responses in yeast cells compared to the control, shown by an up-regulation of stress-specific genes and a down-regulation of lipid biosynthesis, especially ergosterol. By documenting the detrimental effects associated with chemical AFA, we highlight the importance of developing innocuous systems for foam control in industrial fermentation processes.

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Interaction between β-lactoglobulin and structurally different heteroexopolysaccharides investigated by solution scattering and analytical ultracentrifugation study

Knowledge on molecular structure of exopolysaccharides (EPSs) and their roles in the associative interactions with proteins is essential to understand the relationship between their structure, physical and rheological properties. Despite their importance, no detailed molecular characterization of bacterial EPSs and their associative interactions with proteins have been reported up to now. By combining X-ray solution scattering (SAXS), dynamic light scattering (DLS) and analytical ultracentrifugation (AUC) in conjunction with scattering modeling, we have characterized four different heteroexopolysaccharides (HePS-1–HePS-4) from lactic acid bacteria (LAB) and their interactions with β-lactoglobulin. We have previously shown that these HePSs exhibited a compact conformation in solution. Here, SAXS data for HePSs (HePS-1–HePS-4) complexes with β-lactoglobulin showed that β-lactoglobulin aggregated strongly with these HePSs. β-lactoglobulin exists as a dimer at pH 4 in the absence of HePSs. When mixed with HePSs, SAXS analysis showed that β-lactoglobulin formed large aggregates. DLS also showed formation of large aggregates of β-lactoglobulin with HePSs, thus validating SAXS data. Turbidity and AUC data indicated that both soluble and insoluble BLG–HePSs complexes were formed. This study provides new insights into the role of molecular structures in associative interactions between HePSs and BLG which has relevance for various industrial applications.

General information
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Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Department of Chemistry, X-ray Crystallography, Department of Micro- and Nanotechnology, Amphiphilic Polymers in Biological Sensing,
Interactions between host metabolism, immune regulation, and the gut microbiota in diet-associated obesity and metabolic dysfunction

The increase in the prevalence of obesity and obesity-associated complications such as the metabolic syndrome is becoming a global challenge. Dietary habits and nutrient consumption modulates host homeostasis, which manifests in various diet-induced complications marked by changes in host metabolism and immune regulation, which are intricately linked. In addition, diet effectively shapes the gut microbiota composition and activity, which in turn interacts with the host to modulate host metabolism and immune regulation.

In the three studies included in this PhD thesis, we have explored the impact of specific dietary components on host metabolic function, immune regulation and gut microbiota composition and activity. In the first study, we have characterized the effect of a combined high-fat and gliadin-rich diet, since dietary gliadin has been reported to be associated with intestinal inflammation and permeability. The combination of gliadin with an obesogenic diet allowed us to investigate the long-term effects of a single dietary component on host function of obese mice, resulting in identification of notable changes in host metabolic and immune function, as well as in the gut microbiota composition.

In the second study, the effect of a safflower-based high-fat diet on host homeostasis is evaluated, and we show that intake of this n-6 polyunsaturated fatty acid-rich diet exerts only minor host metabolic and inflammatory changes even after 40 weeks intake. Although potentially proinflammatory n-6 polyunsaturated fatty acids are effectively contributing to the liver phospholipids and glucose intolerance manifested after 5 weeks intake, body weight gain, insulin resistance and adipose tissue inflammation are delayed and detectable only after 40 weeks feeding.

In the last study, we evaluated the effect of short-term fasting of obese mice. By applying a coabundance cluster analysis that identifies fasting-induced changes in urine metabolites, gut microbiome and liver lipid composition; we identified defining factors that integrate with the host response to propagate a fasting-induced metabolic shift. The use of multivariate analyses allows for a better understanding of the interplay between diet, host metabolic regulation, immune function and gut microbiota composition and activity. These studies indicate new directions in which to focus further studies to increase our knowledge of host-diet-microbiome interactions.

Investigation of the indigenous fungal community populating barley grains: Secretomes and xylanolytic potential

The indigenous fungal species populating cereal grains produce numerous plant cell wall-degrading enzymes including xylanases, which could play important role in plant-pathogen interactions and in adaptation of the fungi to varying carbon sources. To gain more insight into the grain surface-associated enzyme activity, members of the populating fungal community were isolated, and their secretomes and xylanolytic activities assessed. Twenty-seven different fungal species were isolated from grains of six barley cultivars over different harvest years and growing sites. The isolated fungi were grown on medium containing barley flour or wheat arabinoxylan as sole carbon source. Their secretomes and xylanase activities were analyzed using SDS-PAGE and enzyme assays and were found to vary according to species and carbon sources.
Secretomes were dominated by cell wall degrading enzymes with xylanases and xylanolytic enzymes being the most abundant. A 2-DE-based secretome analysis of Aspergillus niger and the less-studied pathogenic fungus Fusarium poae grown on barley flour and wheat arabinoxylan resulted in identification of 82 A. niger and 31 F. poae proteins many of which were hydrolytic enzymes, including xylanases.

**General information**

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Authors: Sultan, A. (Intern), Frisvad, J. C. (Intern), Andersen, B. (Intern), Svensson, B. (Intern), Finnie, C. (Intern)
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Web of Science (2015): Indexed yes
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Scopus rating (2010): SJR 1.03 SNIP 1.051
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.785 SNIP 0.949
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Scopus rating (2008): SJR 0.739 SNIP 0.856
Scopus rating (2007): SJR 0.51 SNIP 0.755
Scopus rating (2006): SJR 0.618 SNIP 0.679
Scopus rating (2005): SJR 0.525 SNIP 0.766
Scopus rating (2004): SJR 0.697 SNIP 1.001
Scopus rating (2003): SJR 0.615 SNIP 0.762
Scopus rating (2002): SJR 0.801 SNIP 0.511
Isolation, Characterization, and Selection of Molds Associated to Fermented Black Table Olives

Table olives are one of the most important fermented food in the Mediterranean countries. Apart from lactic acid bacteria and yeasts that mainly conduct the olive fermentation, molds can develop on the brine surface, and can have either deleterious or useful effects on this process. From the food safety point of view, occurring molds could also produce mycotoxins, so, it is important to monitor and control them. In this respect, identification of molds associated to two Italian and two Greek fermented black table olives cultivars, was carried out. Sixty strains were isolated and molecularly identified as Penicillium crustosum (21), P. roqueforti (29), P. paneum (1), P. expansum (6), P. polonicum (2), P. commune (1). A group of 20 selected isolates was subjected to technological (beta-glucosidase, cellulolytic, ligninolytic, proteolytic, and xylanolytic activities; proteolytic enzymes) and safety (biogenic amines and secondary metabolites, including mycotoxins) characterization. Combining both technological (presence of desired and absence of undesired enzymatic activities) and safety aspects (no or low production of biogenic amines and regulated mycotoxins), it was possible to select six strains with biotechnological interest. These are putative candidates for future studies as autochthonous co-starters with yeasts and lactic acid bacteria for black table olive production.
Karmitoxin: An amine containing polyhydroxy-polyene toxin from the marine dinoflagellate Karlodinium armiger

Marine algae from the genus Karlodinium are known to be involved in fish-killing events worldwide. Here we report for the first time the chemistry and bioactivity of a natural product from the newly described mixotrophic dinoflagellate Karlodinium armiger. Our work describes the isolation and structural characterization of a new polyhydroxy-polyene named karmitoxin. The structure elucidation work was facilitated by use of 13C enrichment and high-field 2D NMR spectroscopy, where 1H–13C long-range correlations turned out to be very informative. Karmitoxin is structurally related to amphidinols and karlotoxins; however it differs by containing the longest carbon–carbon backbone discovered for this class of compounds, as well as a primary amino group. Karmitoxin showed potent nanomolar cytotoxic activity in an RTgill-W1 cell assay as well as rapid immobilization and eventual mortality of the copepod Acartia tonsa, a natural grazer of K. armiger.
Klinefelter syndrome comorbidities linked to increased X chromosome gene dosage and altered protein interactome activity

Klinefelter syndrome (KS) (47,XXY) is the most common male sex chromosome aneuploidy. Diagnosis and clinical supervision remain a challenge due to varying phenotypic presentation and insufficient characterization of the syndrome. Here we combine health data-driven epidemiology and molecular level systems biology to improve the understanding of KS and the molecular interplay influencing its comorbidities. In total, 78 overrepresented KS comorbidities were identified using in- and out-patient registry data from the entire Danish population covering 6.8 million individuals. The comorbidities extracted included both clinically well-known (e.g., infertility and osteoporosis) and still less established KS comorbidities (e.g., pituitary gland hypofunction and dental caries). Several systems biology approaches were applied to identify key molecular players underlying KS comorbidities: Identification of co-expressed modules as well as central hubs and gene dosage perturbed protein complexes in a KS comorbidity network build from known disease proteins and their protein-protein interactions. The systems biology approaches together pointed to novel aspects of KS disease phenotypes including perturbed Jak-STAT pathway, dysregulated genes important for disturbed immune system (IL4), energy balance...
(POMC and LEP) and erythropoietin signalling in KS. We present an extended epidemiological study that links KS comorbidities to the molecular level and identify potential causal players in the disease biology underlying the identified comorbidities.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, DTU Multi Assay Core, University of Copenhagen
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- Scopus rating (2011): SJR 4.947 SNIP 1.712 CiteScore 7.34
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- BFI (2009): BFI-level 2
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- Scopus rating (2008): SJR 5.737 SNIP 1.72
- Scopus rating (2007): SJR 5.667 SNIP 1.807
- Scopus rating (2006): SJR 5.944 SNIP 1.852
- Scopus rating (2005): SJR 5.575 SNIP 1.972
- Scopus rating (2004): SJR 5.884 SNIP 1.921
- Web of Science (2004): Indexed yes
- Scopus rating (2003): SJR 5.69 SNIP 2.041
- Scopus rating (2002): SJR 6.177 SNIP 1.962
Lactobacillus acidophilus Metabolizes Dietary Plant Glucosides and Externalizes Their Bioactive Phytochemicals

Therapeutically active glycosylated phytochemicals are ubiquitous in the human diet. The human gut microbiota (HGM) modulates the bioactivities of these compounds, which consequently affect host physiology and microbiota composition. Despite a significant impact on human health, the key players and the underpinning mechanisms of this interplay remain uncharacterized. Here, we demonstrate the growth of Lactobacillus acidophilus on mono- and diglucosyl dietary plant glucosides (PGs) possessing small aromatic aglycones. Transcriptional analysis revealed the upregulation of host interaction genes and identified two loci that encode phosphotransferase system (PTS) transporters and phospho-β-glucosidas, which mediate the uptake and deglucosylation of these compounds, respectively. Inactivating these transport and hydrolysis genes abolished or severely reduced growth on PG, establishing the specificity of the loci to distinct groups of PGs. Following intracellular deglucosylation, the aglycones of PGs are externalized, rendering them available for absorption by the host or for further modification by other microbiota taxa. The PG utilization loci are conserved in L. acidophilus and closely related lactobacilli, in correlation with versatile growth on these compounds. Growth on the tested PG appeared more common among human gut lactobacilli than among counterparts from other ecologic niches. The PGs that supported the growth of L. acidophilus were utilized poorly or not at all by other common HGM strains, underscoring the metabolic specialization of L. acidophilus. These findings highlight the role of human gut L. acidophilus and select lactobacilli in the bioconversion of glycoconjugated phytochemicals, which is likely to have an important impact on the HGM and human host.

IMPORTANCE Thousands of therapeutically active plant-derived compounds are widely present in berries, fruits, nuts, and beverages like tea and wine. The bioactivity and bioavailability of these compounds, which are typically glycosylated, are altered by microbial bioconversions in the human gut. Remarkably, little is known about the bioconversion of PGs by the gut microbiota community, despite the significance of this metabolic facet to human health. Our work provides the first molecular insights into the metabolic routes of diet relevant and therapeutically active PGs by Lactobacillus acidophilus and related human gut lactobacilli. This taxonomic group is adept at metabolizing the glucoside moieties of select PG and externalizes their aglycones. The study highlights an important role of lactobacilli in the bioconversion of dietary PG and presents a framework from which to derive molecular insights into their metabolism by members of the human gut microbiota.
Light Sensitivity of Lactococcus lactis Thioredoxin Reductase

The thioredoxin system has evolved in all kingdoms of life acting as a key antioxidant system in the defense against oxidative stress. The thioredoxin system utilizes reducing equivalents from NADPH to reduce protein disulfide targets. The reducing equivalents are shuttled via a flavin and redox active dithiol motif in thioredoxin reductase (TrxR) to reduce the small ubiquitous thioredoxin (Trx). Trx in turn regulates the protein dithiol/disulfide balance by reduction of protein disulfide targets in e.g. ribonucleotide reductase, peroxiredoxins and methionine sulfoxide reductase. The glutathione system is an alternative thiol-based antioxidant system, but the glutathione biosynthesis system is not present in all organisms.

This thesis focuses on the TrxR from the lactic acid bacteria (LAB) model organism Lactococcus lactis ssp. cremoris MG1363, a strain that is glutathione- and catalasenegative, thus expected to rely mainly on the Trx system for thiol-disulfide control. L. lactis is an important industrial microorganism used as starter culture in the dairy production of cheese, buttermilk etc. and known to be sensitive to oxidative stress. The L. lactis TrxR (LlTrxR) is a homodimeric flavoenzyme with each monomer consisting of a FAD- and a NADPH domain. In this type of low molecular weight (LMW) TrxR the NADPH domain rotates 66° relative to the FAD domain in order to complete a catalytic cycle. The TrxR thus exists in two conformations, referred to as FO- and FR-conformation. In the FR-conformation NADPH reduces the FAD co-enzyme, followed by rotation to the FO-conformation in which FADH2 reduces the disulfide in the redox active motif of TrxR. The human TrxR belongs to the high molecular weight (HMW) TrxR involving a selenosulfide pair and functions in a different way than the LMW TrxR, which potentially makes LMW TrxR a therapeutic target.

LlTrxR has been shown to be photo-inactivated by visible light exposure (λmax = 460 nm), which has not been reported in other TrxR and the feature was not observed using the E. coli homolog (EcTrxR) as control. The inactivation coincides with a shift in the absorbance spectrum of the tightly bound FAD co-enzyme and oxidation of the methyl group of the isoalloxazine ring, as determined by MS. The extracted FAD from photo-inactivated LlTrxR also displayed a positive result in a dinitrophenylhydrazine (DNPH) test, indicating the presence of a carbonyl group, i.e. an aldehyde. LlTrxR reduces O2 in the presence of NADPH faster than the EcTrxR and the photo-inactivation is lowered at semi-anaerobic conditions and in the presence of iodine a well-known quencher of photoexcited triplet state flavin.

The present PhD study was initiated in order to identify the underlying functional and structural mechanisms behind this light sensitivity. Crystal structures of photo-inactivated LlTrxR revealed oxidative damages over the course of light exposure. An increased electron density was observed around the carbon-7α of the isoalloxazine ring and to a minor degree around the carbon-8α. The Tyr237 in the vicinity of the flavin was shown to develop increased electron density at C3 position (ortho to the hydroxyl group) as a function of light exposure and was verified by MS to be associated with a +16 Da mass shift, consistent with formation of 3,4-dihydroxyphenylalanine (DOPA). A novel FAD si-face open space was identified in all structures of LlTrxR and predicted to accommodate O2, thus acting as an oxygen pocket. This model explains how the protein-bound FAD can function as a de facto photosensitizer, generating reactive oxygen species (ROS) upon light exposure. Reaction mechanisms accounting for the observed oxidations on FAD and Tyr237 were proposed with the photo-excited isoalloxazine ring generating a superoxide radical (O2•-) at the si-face oxygen pocket. The one-electron deficient isoalloxazine cation can then oxidize Tyr237, which upon deprotonation forms a Tyr phenoxyl radical, a target of superoxide at the C3 position, accounting for the DOPA formation. The superoxide radicals can in addition react with the deprotonated form of carbon-7α of the isoalloxazine, which via a Russel mechanism accounts for the observed aldehyde formation. Another distinct feature of LlTrxR is that it crystallizes mainly in FR-conformation, both with and without NADP+ co-crystallization. LlTrxR was only obtained in FO-conformation in reduced environment during the crystallization in the presence of DTT and absence of NADP+. Interestingly, a mixed FO-FR conformation of the homodimer was also obtained in the presence of phosphate, indicating that the two monomers might function
asynchronously. The oxygen pocket is arising from the Met43 bending way from the si-face towards Pro15. Three methionines, Met18, Met43 and Met67 are bending towards the residue of Pro15 constituting (what in this work is referred to as) a methionine-proline motif.

Identification of key residue surrounding the oxygen pocket makes it possible to predict TrxR from other organisms harboring the FAD si-face oxygen pocket, including organisms such as Bacillus subtilis (BsTrxR) and pathogens such as Staphylococcus aureus (SaTrxR), Streptococcus pyogenes and Bacillus anthracis. A comparative photo-inactivation of TrxR from L. lactis, S. aureus and B. subtilis reveals that SaTrxR and BsTrxR are much less sensitive to light-inactivation than LlTrxR, though SaTrxR exhibited a similar rate of O2 reduction in the presence of NADPH as LlTrxR. Light exposure of L. lactis cell extract showed a prominent drop in TrxR activity and after 12 h about 35% of the LITrxR remained. Preliminary experiments of light exposed living L. lactis cells kept at 4°C, indicate that light exposure is in fact lethal, under the applied conditions. Cell extracts from the same 17 h in vivo irradiated cells showed ~14% remaining TrxR activity. The present investigation shows that TrxR light sensitivity might be a widespread phenomenon among bacteria, particular within the phylum of Firmicutes. This feature can potentially be exploited in clinical light therapy, e.g. in targeted blue light therapy of selected drugresistant pathogenic bacteria.
Lysinibacillus fusiformis M5 induces increased complexity in Bacillus subtilis 168 colony biofilms via hypoxanthine: Running Title: L. fusiformis M5 interaction with B. subtilis 168
In recent years, biofilms have become a central subject of research in the fields of microbiology, medicine, agriculture, or systems biology amongst others. The sociomicrobiology of multispecies biofilms, however, is still poorly understood. Here, we report a screening system that allowed us to identify soil bacteria, which induce architectural changes in biofilm colonies when cocultured with B. subtilis. We identified the soil bacterium Lysinibacillus fusiformis M5 as inducer of wrinkle-formation in B. subtilis colonies mediated by a diffusible signaling molecule. This compound was isolated by bioassay-guided chromatographic fractionation. The elicitor was identified to be the purine hypoxanthine using mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy. We show that the induction of wrinkle formation by hypoxanthine is not dependent on signal recognition by the histidine kinases KinA, KinB, KinC, and KinD, which are generally involved in phosphorylation of the master regulator Spo0A. Likewise, we show that hypoxanthine signaling does not induce the expression of biofilm-matrix related operons epsA-O and tasA-sipW-tapA. Finally, we demonstrate that the purine permease PbuO, but not PbuG, is necessary for hypoxanthine to induce an increase in wrinkle formation of B. subtilis biofilm colonies. Our results suggest that hypoxanthine-stimulated wrinkle development is not due to a direct induction of biofilm-related gene expression, but rather caused by the excess of hypoxanthine within B. subtilis cells, which may lead to cell stress and death.

Importance Biofilms are a bacterial lifestyle with high relevance regarding diverse human activities. Biofilms can be favorable, for instance in crop protection. In nature, biofilms are commonly found as multispecies communities displaying complex social behaviors and characteristics. The study of interspecies interactions will thus lead to a better understanding and use of biofilms as they occur outside laboratory conditions. Here, we present a screening method suitable for the identification of multispecies interactions, and showcase L. fusiformis as a soil bacterium that is able to live alongside B. subtilis and modify the architecture of its biofilms.

**General information**

**State:** Published

**Organisations:** Department of Biotechnology and Biomedicine, Friedrich-Schiller-Universität Jena, Hans Knöll Institute

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Macrophage-derived osteopontin is fragmented by MMP-9 to hinder angiogenesis in the post-myocardial infarction left ventricle

Extracellular matrix (ECM) turnover is a key event during remodeling of the left ventricle (LV) following myocardial infarction (MI). Turnover includes ECM degradation of existing ECM to remove necrotic myocytes and synthesis to produce new ECM to form the infarct scar. Matrix metalloproteinases (MMPs) are elevated post-MI, and MMP-9 has a strong link to post-MI LV dysfunction. The ECM protein osteopontin (OPN) increases post-MI, and we previously identified by mass spectrometry a novel MMP-9 cleavage site of OPN between amino acids 151 and 152. In vitro, peptides both upstream and downstream of the cleavage site increased cardiac fibroblast migration without affecting proliferation.
Meta-analysis of five genome-wide association studies identifies multiple new loci associated with testicular germ cell tumor

The international Testicular Cancer Consortium (TECAC) combined five published genome-wide association studies of testicular germ cell tumor (TGCT; 3,558 cases and 13,970 controls) to identify new susceptibility loci. We conducted a fixed-effects meta-analysis, including, to our knowledge, the first analysis of the X chromosome. Eight new loci mapping to
2q14.2, 3q26.2, 4q35.2, 7q36.3, 10q26.13, 15q21.3, 15q22.31, and Xq28 achieved genome-wide significance (P < 5 × 10−8). Most loci harbor biologically plausible candidate genes. We refined previously reported associations at 9p24.3 and 19p12 by identifying one and three additional independent SNPs, respectively. In aggregate, the 39 independent markers identified to date explain 37% of father-to-son familial risk, 8% of which can be attributed to the 12 new signals reported here. Our findings substantially increase the number of known TGCT susceptibility alleles, move the field closer to a comprehensive understanding of the underlying genetic architecture of TGCT, and provide further clues to the etiology of TGCT.

General information
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Organisations: Department of Biotechnology and Biomedicine, DTU Multi Assay Core, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Department of Systems Biology, National Institutes of Health, University of Leeds, Cancer Registry of Norway, Oslo and Akershus University College of Applied Sciences, Karolinska Institutet, The Institute of Cancer Research, University of Pennsylvania, Fred Hutchinson Cancer Research Center, Institute for Systems Biology, Harvard University, H. Lee Moffitt Cancer Center and Research Institute, Copenhagen University Hospital
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Metabolic characterization and transformation of the non-dairy Lactococcus lactis strain KF147, for production of ethanol from xylose

The non-dairy lactic acid bacterium Lactococcus lactis KF147 can utilize xylose as the sole energy source. To assess whether KF147 could serve as a platform organism for converting second generation sugars into useful chemicals, we characterized growth and product formation for KF147 when grown on xylose. In a defined medium KF147 was found to co-metabolize xylose and arginine, resulting in bi-phasic growth. Especially at low xylose concentrations, arginine significantly improved growth rate. To facilitate further studies of the xylose metabolism, we eliminated arginine catabolism by deleting the arcA gene encoding the arginine deiminase. The fermentation product profile suggested two routes for xylose degradation, the phosphoketolase pathway and the pentose phosphate pathway. Inactivation of the phosphoketolase pathway redirected the entire flux through the pentose phosphate pathway whereas over-expression of phosphoketolase increased the flux through the phosphoketolase pathway. In general, significant amounts of the mixed-acid products, including lactate, formate, acetate and ethanol, were formed irrespective of xylose concentrations. To demonstrate the potential of KF147 for converting xylose into useful chemicals we chose to redirect metabolism towards ethanol production. A synthetic promoter library was used to drive the expression of codon-optimized versions of the Zymomonas mobilis genes encoding pyruvate decarboxylase and alcohol dehydrogenase, and the outcome was a strain producing ethanol as the sole fermentation product with a high yield corresponding to 83% of the theoretical maximum. The results clearly indicate the great potential of using the more metabolically diverse non-dairy L. lactis strains for bio-production based on xylose containing feedstocks.

General information
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Organisations: Department of Systems Biology, National Food Institute, Research Group for Microbial Biotechnology and Biorefining, Department of Biotechnology and Biomedicine, Metabolic Signaling and Regulation
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Main Research Area: Technical/natural sciences
Metabolic engineering of yeast for fermentative production of flavonoids

Yeast Saccharomyces cerevisiae was engineered for de novo production of six different flavonoids (naringenin, liquiritigenin, kaempferol, resokaempferol, quercetin, and fisetin) directly from glucose, without supplementation of expensive intermediates. This required reconstruction of long biosynthetic pathways, comprising up to eight heterologous genes from plants. The obtained titers of kaempferol 26.57±2.66mgL^{-1} and quercetin 20.38±2.57mgL^{-1} exceed the previously reported titers in yeast. This is also the first report of de novo biosynthesis of resokaempferol and fisetin in yeast. The work demonstrates the potential of flavonoid-producing yeast cell factories.
Dementia and type 2 diabetes are both characterized by long prodromal phases challenging the study of potential risk factors and their temporal relation. The progressive relation between metabolic syndrome, insulin resistance, and dementia has recently been questioned, wherefore the aim of this study was to assess the potential association between these precursors of type 2 diabetes and cognitive dysfunction. Using data from the Prospective Epidemiological Risk Factor study (n=2,103), a prospective study of elderly women in Denmark, we found that impaired fasting plasma glucose was associated with 44% (9%-91%) larger probability of developing cognitive dysfunction. In addition subjects above the HOMA-IR threshold (HOMA-IR > 2.6) had 47% (9%-99%) larger odds of cognitive dysfunction. The associations could indicate that a significant proportion of dementia cases in women is likely to be preventable by effective prevention and control of the insulin homeostasis.
Phage therapy has regained interest in recent years due to the alarming spread of antibiotic resistance. Whilst phage cocktails are commonly sold in pharmacies in countries such as Georgia and Russia, this is not the case in western countries due to western regulatory agencies requiring a thorough characterization of the drug. Here, DNA sequencing of constituent biological entities constitutes a first step. The pyophage (PYO) cocktail is one of the main commercial products of the Georgian Eliava Institute of Bacteriophage, Microbiology and Virology and is used to cure skin infections. Since its first production in the 1930s, the composition of the cocktail has been periodically modified to add phages effective against emerging pathogenic strains. In this paper, we compared the composition of three PYO cocktails from 1997 (PYO97), 2000 (PYO2000) and 2014 (PYO2014). Based on next generation sequencing, de novo assembly and binning of contigs into draft genomes based on tetranucleotide distance, thirty and twenty-nine phage draft genomes were predicted in PYO97 and PYO2014, respectively. Of these, thirteen and fifteen shared high similarity to known phages. Eleven draft genomes were found to be common in the two cocktails. One of these showed no similarity to publicly available phage genomes. Representatives of phages targeting E. faecalis, E. faecium, E. coli, Proteus, P. aeruginosa and S. aureus were found in both cocktails. Finally, we estimated larger overlap of the PYO2000 cocktail to PYO97 compared to PYO2014. Using next generation sequencing and metagenomics analysis, we were able to characterize and compare the content of PYO cocktails separated by 17 years in time. Even though the cocktail composition is upgraded every six months, we found it to remain relatively stable over the years.
Microbial platform for production of aromatic compounds

Polyketides form the basic building blocks of numerous natural products, which are in use in pharmaceuticals, food additives and other fine chemicals. Many of these polyketides possess very specific cyclic and aromatic conformations. The programmable platform we aim to create will be able to efficiently and directly produce a vast array of polyketide derived compounds. The platform will be integrated in a well known heterologous host to improve the predictability and engineering options of the platform.

The basic platform will allow production of polyketides of different lengths and folding patterns. The biosynthesis of the polyketides is divided into different steps and by swapping either domains between enzymes or whole enzymes between pathways the length of the polyketides or the individual folding pattern can be directed towards a desired product. Further development of the platform will be combinations of more enzymes to enlarge the possible chemical diversity of the platform.

General information

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Organisations: Department of Biotechnology and Biomedicine, Biosynthetic Pathway Engineering, Natural Product Discovery
Authors: Skovbjerg, C. A. E. (Intern), Olsen, K. J. K. (Intern), Larsen, T. O. (Intern), Frandsen, R. J. N. (Intern)
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Mikrobiologisk kvalitet af minkfoder

enkelte råvarer og dermed potentielle til at foderet fordærver ved uhensigtsmæssig opbevaring og anvendelse på minkgårdene. Der blev fundet MRSA og Salmonella i svineprodukter, men ikke i færdigvarer. Derudover blev der i enkelte af de vegetabilske råvarer fundet svampetoksiner, der er kendt for at forårsage sygdomme i andre dyr. De anvendte metoder har en naturlig begrænsning, da der kun undersøges en mikroskopisk del af de store mængder af råvarer, der anvendes dagligt. Da råvaresammensætningen konstant er under forandring, bør mulige cocktaileffekter overvejes ved introduktion af nye typer råvarer.

**General information**

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Authors: Lyhs, U. (Intern), Nonnemann, B. (Intern), Hjulsager, C. K. (Intern), Pedersen, K. (Intern), Chriél, M. (Intern), Frandsen, H. L. (Intern), Andersen, B. (Intern)

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Model-based analysis of N-glycosylation in Chinese hamster ovary cells

The Chinese hamster ovary (CHO) cell is the gold standard for manufacturing of glycosylated recombinant proteins for production of biotherapeutics. The similarity of its glycosylation patterns to the human versions enable the products of this cell line favorable pharmacokinetic properties and lower likelihood of causing immunogenic responses. Because glycan structures are the product of the concerted action of intracellular enzymes, it is difficult to predict a priori how the effects of genetic manipulations alter glycan structures of cells and therapeutic properties. For that reason, quantitative models able to predict glycosylation have emerged as promising tools to deal with the complexity of glycosylation processing. For example, an earlier version of the same model used in this study was used by others to successfully predict changes in enzyme activities that could produce a desired change in glycan structure. In this study we utilize an updated version of this model to provide a comprehensive analysis of N-glycosylation in ten Chinese hamster ovary (CHO) cell lines that include a wild type parent and nine mutants of CHO, through interpretation of previously published mass spectrometry data. The updated N-glycosylation mathematical model contains up to 50,605 glycan structures. Adjusting the enzyme activities in this model to match N-glycan mass spectra produces detailed predictions of the glycosylation process, enzyme activity profiles and complete glycosylation profiles of each of the cell lines. These profiles are consistent with biochemical and genetic data reported previously. The model-based results also predict glycosylation features of the cell lines not previously published, indicating more complex changes in glycosylation enzyme activities than just those resulting directly from gene mutations. The model predicts that the CHO cell lines possess regulatory mechanisms that allow them to adjust glycosylation enzyme activities to mitigate side effects of the primary loss or gain of glycosylation function known to exist in these mutant cell lines. Quantitative models of CHO cell glycosylation have the potential for predicting how glycoengineering manipulations might affect glycoform distributions to improve the therapeutic performance of glycoprotein products.
Modifiable risk factors promoting neurodegeneration is associated with two novel brain degradation markers measured in serum

There has been limited success with blood-based biomarkers of neurodegeneration. One perceived reason is that blood has no direct contact to the brain. Recently developed blood-based biomarkers of tau-degradation have shown promise as potential tools for peripheral assessment of neurodegeneration; however, factors contributing to the levels of these in
blood are poorly understood. Using multiple linear regression analysis in cross-sectional data from an observational cohort (n = 5626), the aim was to examine which factors correlate to the serological levels of two novel biomarkers measuring truncated tau fragments (Tau-A and Tau-C) in serum. Platelets, albumin and several modifiable risk factors, including Body Mass Index, high density lipoprotein and White Blood Cell count were associated with the serum level of tau fragments. The factors associated with tau in serum may promote neurodegeneration and alter the permeability of the Blood Brain Barrier through chronic inflammation and vascular dysfunction. These data are of key importance for understanding the mechanism of release and subsequent peripheral processing of tau from the brain and will assist in the development of future blood-based biomarkers.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, Department of Systems Biology, Center for Biological Sequence Analysis, Regulatory Genomics, Disease Systems Immunology, Nordic Bioscience A/S, ProScion A/S

Authors: Neergaard, J. (Intern), Møller, K. D. (Intern), Christiansen, C. (Ekstern), Nielsen, H. B. (Ekstern), Workman, C. (Intern), Pedersen, S. B. (Intern), Henriksen, K. (Ekstern), Karsdal, M. A. (Ekstern)

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Blood brain barrier, Blood-based biomarkers, Neurodegeneration, Tau
Modulation of Cartilage Degradation Biomarkers Reflect the Activation and Inhibition of Pro-Inflammatory Cytokine Signaling in an Ex Vivo Model of Bovine Cartilage

Background/Purpose: Several inflammatory cytokines and intracellular signaling pathways have been targeted in drug development with varying clinical results. Improved understanding of the intracellular signaling's modulation of the extracellular matrix turnover could aid in selecting novel anti-inflammatory treatments for inflammatory arthritis. The aim of this study was to investigate the effect of small molecule inhibitors targeting 4 main pro-inflammatory signaling pathways (p38, Syk, IκBα, and STAT) on Oncostatin M (OSM) and Tumor Necrosis Factor α (TNFα) stimulated cartilage.

General information
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Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, University of Copenhagen, Nordic Bioscience A/S
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Molecular diagnostics of aleutian mink disease virus: applied use of next generation sequencing and phylogenetics

Aleutian Mink Disease virus (AMDV) is a parvovirus causing Aleutian Mink Disease (AMD), often referred to as plasmacytosis. It is a systemic infection affecting mink of all ages, and is globally the most important pathogen impacting mink farming. In Denmark AMDV has since 1999 been monitored by a national control program, which is based on serological screening of all animals and encourages infected farms to stamp out. Historically there has been no consensus about which genomic region of the virus to analyse e.g. in relation to surveillance, and most previous studies in this regard, have been based either on partial or entire genes, or on pure epidemiological data. Thus, when initiating this project, little was known about AMDV’s total genomic diversity and how the virus was spread between farms.

Recent advances in the field of molecular diagnostics have made high throughput tools such as next generation sequencing cheaper and more easily available. Whole genome sequencing and advanced phylogenetic analyses have successfully been applied to describe the molecular evolution and transmission patterns for viruses such as Foot and Mouth Disease Virus (FMDV), Ebola, and avian influenza virus, however not previously for AMDV. The overall aim with this thesis was to investigate if next generation sequencing and phylogenetic analyses of full length isolates could improve our understanding of the total genomic diversity and evolution of AMDV. Additionally, we wanted to evaluate if this knowledge could contribute to the elucidation of AMDV transmission between farms and improve molecular diagnostics. During the first phase of this project a method for performing whole genome sequencing of AMDV was developed. This protocol enabled the sequencing of a large number of in vivo infectious AMDV isolates and provided the necessary dataset to act as foundation for the remaining analyses in the thesis. The first original paper (Manuscript 1) describes this protocol.

Manuscript 2 is a proof-of-concept study which demonstrated the advantage of using the whole genome sequence approach, compared to the in Denmark traditionally used partial NS1 gene sequencing, for the elucidation of transmission pathways between farms. The study was performed on samples from a small local AMDV outbreak, and clearly illustrated that the phylogenies based on partial NS1 gene sequencing were uninformative and could not be used for determining transmission pathways, even in the light of supporting epidemiological data. The whole-genome approach on the other hand, confirmed the epidemiological hypothesis about the direction of spread.

In Manuscript 3, the methodologies from Manuscript 1 and 2 were applied to generate the to-date most comprehensive phylogenetic and genetic analysis of full-length AMDV isolates, composed of more than 200 field strains. The study shed light on the diversity and evolutionary behaviour of two distinct AMDV strains, in addition to providing the first robust evolutionary rate-estimates. Altogether, the work presented in this thesis provides a contribution to the molecular diagnostics of AMDV, enables us better to understand the virus’ evolutionary behaviour in the context of mink farming, and is anticipated to be of value for more accurately tracing back in time the emergence of future outbreaks.

General information
State: Published
Organisations: Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Department of Biotechnology and Biomedicine, National Veterinary Institute, Virology, Kopenhagen Diagnostics
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Mucin- and carbohydrate-stimulated adhesion and subproteome changes of the probiotic bacterium Lactobacillus acidophilus NCFM

Adhesion to intestinal mucosa is a crucial property for probiotic bacteria. Adhesion is thought to increase host-bacterial interactions, thus potentially enabling health benefits to the host. Molecular events connected with adhesion and surface proteome changes were investigated for the probiotic Lactobacillus acidophilus NCFM cultured with established or emerging prebiotic carbohydrates as carbon source and in the presence of mucin, the glycoprotein of the epithelial mucus layer. Variation in adhesion to HT29-cells and mucin was associated with carbon source and mucin-induced subproteome abundance differences. Specifically, while growth on fructooligosaccharides (FOS) only stimulated adhesion to intestinal HT-29 cells, cellobiose and polydextrose in addition increased adhesion to mucin. Adhesion to HT-29 cells increased by about 2-fold for bacteria grown on mucin-supplemented glucose. Comparative 2DE-MS surface proteome analysis showed different proteins in energy metabolism appearing on the surface, suggesting they exert moonlighting functions. Mucin-supplemented bacteria had relative abundance of pyruvate kinase and fructose-bisphosphate aldolase increased by about 2-fold while six spots with 3.2-2.1 fold reduced relative abundance comprised elongation factor G, phosphoglycerate kinase, BipAEFTU family GTP-binding protein, ribonucleoside triphosphate reductase, adenylosuccinate synthetase, 30S ribosomal protein S1, and manganese-dependent inorganic pyrophosphatase. Surface
proteome of cellobiose- compared to glucose-grown L. acidophilus NCFM had phosphate starvation inducible protein
stress-related, thermostable pullulanase, and elongation factor G increasing 4.4-2.4 fold, while GAPDH, elongation factor
Ts, and pyruvate kinase were reduced by 2.0-1.5 fold in relative abundance. Addition of recombinant L. acidophilus NCFM
elongation factor G and pyruvate kinase to a coated mucin layer significantly suppressed subsequent adhesion of the
bacterium. Biological significance: Human diet is important for intestinal health and food components, especially non-
igestible carbohydrates can beneficially modify the microbiota. In the present study, effects of emerging and established
prebiotic carbohydrates on the probiotic potential of Lactobacillus acidophilus NCFM were investigated by testing adhesion
to a mucin layer and intestinal cells, and comparing this with changes in abundance of surface proteins thought to be
important for host interactions. Increased adhesion was observed following culturing of the bacterium with
fructooligosaccharides, cellobiose or polydextrose, as well as mucin-supplemented glucose as carbon source. Enhanced
adhesion ability can prolong bacterial residence in GIT yielding positive health effects. Higher relative abundance of
certain surface proteins under various conditions (i.e. grown on cellobiose or mucin-supplemented glucose) suggested
involvement of these proteins in adhesion, as confirmed by competition in case of two recombinantly produced
moonlighting proteins. Combination of Lactobacillus acidophilus NCFM with different carbohydrates revealed potential
bacterial determinants of symbiotic interactions, including stimulation of adhesion.

General information
State: Published
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Immunology, Protein Glycoscience and Biotechnology, Technical University of Denmark, DuPont Nutrition and Health
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(Intern), Abou Hachem, M. (Intern), Svensson, B. (Intern)
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Network reconstruction of the mouse secretory pathway applied on CHO cell transcriptome data

Background: Protein secretion is one of the most important processes in eukaryotes. It is based on a highly complex machinery involving numerous proteins in several cellular compartments. The elucidation of the cell biology of the secretory machinery is of great importance, as it drives protein expression for biopharmaceutical industry, a 140 billion USD global market. However, the complexity of secretory process is difficult to describe using a simple reductionist approach, and therefore a promising avenue is to employ the tools of systems biology.

Results: On the basis of manual curation of the literature on the yeast, human, and mouse secretory pathway, we have compiled a comprehensive catalogue of characterized proteins with functional annotation and their interconnectivity. Thus we have established the most elaborate reconstruction (RECON) of the functional secretion pathway network to date, counting 801 different components in mouse. By employing our mouse RECON to the CHO-K1 genome in a comparative genomic approach, we could reconstruct the protein secretory pathway of CHO cells counting 764 CHO components. This RECON furthermore facilitated the development of three alternative methods to study protein secretion through graphical visualizations of omics data. We have demonstrated the use of these methods to identify potential new and known targets for engineering improved growth and IgG production, as well as the general observation that CHO cells seem to have less strict transcriptional regulation of protein secretion than healthy mouse cells.

Conclusions: The RECON of the secretory pathway represents a strong tool for interpretation of data related to protein secretion as illustrated with transcriptomic data of Chinese Hamster Ovary (CHO) cells, the main platform for mammalian protein production.
Nitrification, the biological oxidation of ammonium to nitrate, is a fundamental process in the nitrogen cycle and plays an important role in natural and engineered systems. Throughout the last century, nitrification was assumed to be a two-step process executed by two different functional groups, ammonia oxidizing prokaryotes (AOP) and nitrite oxidizing bacteria (NOB). Recently, several articles have shown the capability of a single microorganism, belonging to the genus Nitrospira, to carry out the complete oxidation of ammonia to nitrate (comammox). Nitrospira spp. are widespread in both natural and engineered ecosystems associated with nitrogen cycling and different species are frequently observed to coexist in the same environment. Besides recent discoveries pointing towards versatile metabolism in some Nitrospira species, little is known about the functional potential of the two comammox Nitrospira clades, and the factors involved in niche-partitioning between comammox and canonical Nitrospira.
A comparative genomics analysis was conducted with five genomes recovered from a groundwater-fed rapid sand filter (including both comammox clades and a nitrite-oxidizing Nitrospira population genome) and high quality published Nitrospira genomes, to reveal distinct genomic features within Nitrospira. In addition, we investigated the evolution of the ammonia oxidation pathway in comammox Nitrospira. This analysis revealed distinct genetic capabilities of the different comammox clades and canonical Nitrospira which can help to explain the coexistence and niche partitioning of Nitrospira spp. These divergences range from the nitrogen source utilization capacity to the ability for electron donor versatility, and other characteristics such as stress response. With respect to the evolutionary history of comammox Nitrospira, our analysis indicates transfer events with betaproteobacterial ammonia oxidizers. In addition, transfer events between comammox clade A and clade B were also detected for genes belonging to the ammonium oxidation pathway. Together, these results expand the actual knowledge of the ecology and evolution of the recently discovered comammox Nitrospira.

General information
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Organisations: Department of Environmental Engineering, Water Technologies, Department of Biotechnology and Biomedicine, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, Metagenomics
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Nomenclature for alleles of the human carboxylesterase 1 gene

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Scopus rating (2011): SJR 1.315 SNIP 1.109 CiteScore 3.93
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.479 SNIP 1.081
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Scopus rating (2009): SJR 1.593 SNIP 1.146
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Non-invasive evaluation of extracellular matrix remodeling in peripheral artery disease

General information
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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Hospital Universitari Sant Joan, Nordic Bioscience A/S
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Scopus rating (2015): CiteScore 3.71
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Non-invasive quantification of collagen turnover in renal transplant recipients

Kidney allograft failure due to chronic injury/rejection remains the main cause of graft loss in renal transplant recipients (RTR). Here, we investigated whether specific biomarkers of extracellular matrix (ECM) turnover are associated with allograft function and chronic kidney disease (CKD) stage in RTR. Seventy-eight patients who attended the University Medical Center Groningen for a routine check-up after kidney transplantation were enrolled in the study. Plasma and/or 24h-urine samples were collected and specific matrix-metalloproteinase-generated neo-epitope fragments of collagens were measured by enzyme-linked immunosorbent assay. Our results demonstrated that urinary levels of C3M, a marker for collagen type III degradation, correlated with estimated glomerular filtration rate (eGFR; r = 0.58, p<0.0001), with lower levels detected in the urine of patients with advanced CKD. In addition, plasma levels of Pro-C6, a marker for collagen type VI formation, significantly increased with disease progression and correlated with eGFR (r = -0.72, p<0.0001). Conversely, plasma C3M and urinary Pro-C6 levels showed no correlation with renal function. We identified two neo-epitope biomarkers of tissue turnover associated with ECM remodeling and fibrosis that can stratify patients by CKD stage. This is as promising first step towards non-invasive monitoring of ECM turnover in the kidneys.

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Noninvasive Sampling of Mucosal Lining Fluid for the Quantification of In Vivo Upper Airway Immune-mediator Levels

This protocol describes noninvasive sampling of undisturbed upper airway mucosal lining fluid. It also details the extraction procedure used prior to the analysis of immune mediators in fluid eluates for the study of the airway topical immune signature, without the need for stimulation procedures (often used by other techniques). The mucosal lining fluid is sampled on a strip of filter paper placed at the anterior part of the inferior turbinate and left for 2 min of absorption. Analytes are eluted from the filter papers, and the extracted protein-based eluates are analyzed by an electrochemiluminescence-based immunoassay, allowing for the high-sensitivity quantification of low- and high-level analytes in the same sample. We measured the in vivo levels of 20 preselected immune mediators related to specific immune signaling pathways in the upper airway mucosa, but the technique is not limited to that specific panel or sampling site. The technique was first implemented in 7-year-old children from the Copenhagen Prospective Studies on Asthma in Childhood2000 (COPSAC2000) cohort with allergic rhinitis. It was thereafter used in the longitudinal COPSAC2010 birth cohort, sampled at 1 month, 2 years, and 6 years of age and at instances of acute respiratory symptoms. We successfully
obtained and analyzed samples from 620 (89%) of 700 1-month-old children; a few samples were below the assay detection limit (reported as the median (Inter-Quartile Range (IQR)). The number of samples below the detection limit (i.e. from 0 to the set point for the lower limit of detection) for each mediator was 29 (7.25 - 119.5). This technique enables the quantification of the in vivo airway mucosal immune profile from birth, can be applied longitudinally, and can be applied to studies on the effect of genetics and early-life environmental exposures, pathophysiology, endotyping, and monitoring of respiratory diseases, and development and evaluation of novel therapeutics.

General information
State: Published
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Scopus rating (2016): CiteScore 0.78 SJR 0.867 SNIP 0.431
Web of Science (2016): Indexed yes
Scopus rating (2015): SJR 0.803 SNIP 0.403 CiteScore 0.59
BFI (2014): BFI-level 1
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Scopus rating (2013): SJR 0.841 SNIP 0.455 CiteScore 0.63
ISI indexed (2013): ISI indexed no
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Novel biomarkers of changes in muscle mass or muscle pathology
Muscle protein turnover is a dynamic equilibrium that regulates the body composition and homeostasis through various cytokines and proteases. When the balance between protein synthesis and protein degradation is altered, proper muscle function and regeneration are being hampered, affecting patient’s quality of life. In these conditions, a constellation of symptoms as inflammation, fibrosis and muscle wasting has been widely observed despite different onsets. Many of these pathologies are incurable and can only be treated symptomatically. A wide array of biomarkers has been used to monitor qualitative and quantitative changes in muscle. Unfortunately, there has not been an ideal panel of biomarkers that can be readily applied in studies and assist with prognosis of the disease or response to treatment. Protein biomarkers in serum are easily obtainable, not as invasive as other methods and can be used as targets for sensitive antibody-based assays. The overall hypothesis is that both the ECM and myofibrillar biomarkers are released in circulation of people with muscle pathologies and can be used to develop bioassays. We wanted to test if those protein fingerprint biomarkers can characterize and distinguish between healthy individuals and patients with different myopathy diseases, describe the underlying mechanisms of muscle conditions and possibly putative response to an intervention. There were three different studies where biomarkers were applied in this thesis. Study I involved 51 myositis patients (28 Dermatomyositis, DM and 23 Polymyositis, PM) compared to a control group. A range of biomarkers derived from cleavage of collagens I (C1M and PINP), III (C3M and PRO-C3), VI (C6M) and C-reactive protein (CRPM) was applied to distinguish between the diseases
in this cross-sectional cohort. Both DM and PM significantly affect several of the biomarkers levels measured in this study, most prominently CRP and PINP, indicative of significantly altered turnover of extracellular matrix components and CRP. C3M correlated with Interferon gene score, in PM and DM, and CRP with MMT8 score in DM. We further developed an assay directed at the C-terminal of troponin T1 (TNNT1) that was measured in studies II and III. In study II, a group of cancer patients after radiotherapy was admitted to a resistance-training program alongside to a control group that followed the same training regime. Serum samples were obtained right after radiotherapy, before and during the training period. TNNT1 levels were significantly elevated in the patient group compared to the control group, even before engaging in any form of physical activity. After engaging in physical training, the biomarker levels further increased through time, reaching a significant difference both compared to the patients baseline (T24 vs T0, p<0.05) as well as to the control group (T1 and T24 vs control, p<0.0001). In study III, healthy subjects were put in 56 days of bed rest, split in a group with resistance vibration exercise as a countermeasure and a group with no countermeasure at all. After the bed rest period, both groups entered the same rehabilitation process for a period of 128 days. There was a significant difference between the two groups in the bed rest stage that demonstrates a distinct response to the RVE counter measure. The increased levels of circulating TNNT1 for the RVE group in this study could be explained by the unloading of troponin from the muscle. During the remobilization stage, the TNNT1 levels were increased significantly in both groups in a very similar manner, compared to the baseline as well as the levels during the bed rest period. In day 28 of recovery were the maximum levels of TNNT1 observed and by the time of training completion, the levels were almost returned back to baseline. The results of this thesis point to the fact that that a panel of biomarkers could fill in the need to characterize complex processes in rare neuromuscular diseases. Addressing the main manifestation of the diseases in well-described clinical cohorts could expedite pharmaceutical trials and provide valuable information on the pathology of the disease.

General information
State: Published
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Novel genes involved in pathophysiology of gonadotropin-dependent adrenal tumors in mice
Specific inbred strains and transgenic inhibin-α Simian Virus 40 T antigen (inha/Tag) mice are genetically susceptible to gonadectomy-induced adenocortical neoplasias. We identified altered gene expression in prepubertally gonadectomized (GDX) inha/Tag and wild-type (WT) mice. Besides earlier reported Gata4 and Lhcr, we found up-regulated Esr1, Prfr-rs1, and down-regulated Grb10, Mmp24, Sgcd, Rerg, Gnas, Nfatc2, Gnrhr, Igf2 in inha/Tag adrenal tumors. Sex-steroidogenic enzyme genes expression (Srd5a1, Cyp19a1) was up-regulated in tumors, but adrenal-specific steroidogenic enzyme (Cyp21a1, Cyp11b1, Cyp11b2) down-regulated. We localized novel Lhcr transcripts in adrenal cortex parenchyma and in non-steroidogenic A cells, in GDX WT and in intact WT mice. We identified up-regulated Esr1 as a potential novel biomarker of gonadectomy-induced adenocortical tumors in inha/Tag mice presenting with an inverted adrenal-to-gonadal steroidogenic gene expression profile. A putative normal adrenal remodeling or tumor suppressor role of the down-regulated genes (e.g. Grb10, Rerg, Gnas, and Nfatc2) in the tumors remains to be addressed.

General information
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O2 affects the activity of amikacin on mycobacterium abscessus biofilm

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Pages: 359-360
Obesity is associated with depot-specific alteration in adipocyte DNA methylation and gene expression

The present study aimed to identify genes exhibiting concomitant obesity-dependent changes in DNA methylation and gene expression in adipose tissues in the mouse using diet-induced obese (DIO) C57BL/6J and genetically obese ob/ob mice as models. Mature adipocytes were isolated from epididymal and inguinal adipose tissues of ob/ob and DIO C57BL/6J mice. DNA methylation was analyzed by MeDIP-sequencing and gene expression by microarray analysis. The majority of differentially methylated regions (DMRs) were hypomethylated in obese mice. Global methylation of long interspersed elements indicated that hypomethylation did not reflect methyl donor deficiency. In both DIO and ob/ob mice, we observed more obesity-associated methylation changes in epididymal than in inguinal adipocytes. Assignment of DMRs to promoter, exon, intron and intergenic regions demonstrated that DIO-induced changes in DNA methylation in C57BL/6J mice occurred primarily in exons, whereas inguinal adipocytes of ob/ob mice exhibited a higher enrichment of DMRs in promoter regions than in other regions of the genome, suggesting an influence of leptin on DNA methylation in inguinal adipocytes. We observed altered methylation and expression of 9 genes in epididymal adipocytes, including the known obesity-associated genes, Ehd2 and Kctd15, and a novel candidate gene, Irf8, possibly involved in immune type 1/type2 balance. The use of 2 obesity models enabled us to dissociate changes associated with high fat feeding from those associated with obesity per se. This information will be of value in future studies on the mechanisms governing the development of obesity and changes in adipocyte function associated with obesity.

General information

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Organisations: Department of Systems Biology, DTU Multi Assay Core, Department of Biotechnology and Biomedicine, DTU Multi Assay Core, Department of Bio and Health Informatics, Disease Intelligence and Molecular Evolution, University of Copenhagen, BGI-Shenzhen, National Institute for Nutrition and Seafood Research, University of California, San Francisco
Authors: Sonne, S. B. (Ekstern), Yadav, R. (Intern), Yin, G. (Ekstern), Dalgaard, M. D. (Intern), Myrmel, L. S. (Ekstern), Gupta, R. (Intern), Wang, J. (Ekstern), Madsen, L. (Ekstern), Kajimura, S. (Ekstern), Kristiansen, K. (Ekstern)
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Objective Cognitive Impairment and Progression to Dementia in Women: The Prospective Epidemiological Risk Factor Study

Background: Identification of subjects with a progressive disease phenotype is an urgent need in the pharmaceutical industry where most of the recent clinical trials in Alzheimer’s disease have failed. Objectives: The objective of this study was to identify subgroups of individuals with objective cognitive impairment (OCI), who were most likely to progress to dementia and to identify the risk factors associated with progression. Design: Prospective cohort study. Setting: Population-based. Participants: 5,380 elderly women from Denmark. Measurements: The Short Blessed Test and a category fluency test with animal naming, was used to assess cognitive function, and to classify them into different groups of OCI. Results: OCI was identified in 852 subjects at baseline. The risk of dementia was elevated for OCI subjects as compared to subjects with normal cognition (HR 1.46[1.19-1.79]). The courses of OCI were studied in a sub-cohort who completed the cognitive assessment at both the baseline and the follow-up visit (n = 1,933). Of these subjects 203 had OCI at baseline. The multi-domain subtypes of OCI were associated with progressive OCI. Subjects most likely to
progress were older, physically inactive, had a higher level of total cholesterol (>6.5 mmol/L) and had a history of depression as compared to subjects with a non-progressive course of OCI. Conclusions: In this cohort we identified a risk profile associated with progression from OCI in older women. The degree of impairment at baseline was an important predictor of conversion to dementia, additionally several modifiable risk factors were associated with progression.

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**Optimization of tolerability and efficacy of the novel dual amylin and calcitonin receptor agonist KBP-089 through dose escalation and combination with a GLP-1 analog**
Amylin and GLP-1 agonism induce a well-known anorexic effect at dose initiation, which is managed by dose escalation. In this study we investigated how to optimize tolerability while maintaining efficacy of a novel, highly potent dual amylin and calcitonin receptor agonist (DACRA), KBP-089. Furthermore, we tested the GLP-1 add-on potential of KBP-089 in high-fat diet (HFD)-fed rats. KBP-089 potently activated both the amylin and calcitonin receptors in vitro and demonstrated a prolonged receptor activation as well as a potent reduction of acute food intake. HFD rats dosed every day or every second day obtained equal weight loss at study end, albeit with an uneven reduction in both food intake and body weight in rats dosed every second day. In a 4-fold dose escalation, KBP-089 induced a transient reduction in food intake at every escalation step, with reducing magnitude over time, and the following treatment with 2.5, 10, and 40 µg/kg resulted in an ~15% vehicle-corrected weight loss, a corresponding reduction in adipose tissue (AT), and, in all treatment groups, improved oral glucose tolerance (P < 0.01). Twofold and linear escalations suppressed body weight evenly with no significant reduction in food intake at either escalation step. KBP-089 (1.25 µg/kg) and liraglutide (50 µg/kg) reduced 24-h food intake by 29% and 37% compared with vehicle, respectively; however, when they were combined, 24-h food intake was reduced by 87%. Chronically, KBP-089 (1.25 µg/kg) and liraglutide (50 µg/kg) lowered body weight 8% and 2% in HFD rats, respectively, whereas the combination resulted in a 12% body weight reduction. Moreover, the combination improved glucose tolerance (P < 0.05). In conclusion, DACRAs act complementarily with GLP-1 on food intake and body weight. Furthermore, on escalation, KBP-089 was well tolerated and induced and sustained a significant weight loss and a reduction in AT in lean and HFD rats, underscoring the potential of KBP-089 as an anti-obesity agent.

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Organisations: Department of Biotechnology and Biomedicine, Systems Metabolic Lipidology, Technical University of Denmark, Nordic Bioscience A/S
Authors: Gydesen, S. (Ekstern), Andreassen, K. V. (Ekstern), Hjuler, S. T. (Ekstern), Hellgren, L. (Intern), Karsdal, M. A. (Ekstern), Henriksen, K. (Ekstern)
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Glioblastoma is a devastating disease and despite extensive treatment, overall survival (OS) for these patients remains poor. Yet, a small proportion of glioblastoma patients present relatively long survival over 3 years, but the underlying molecular background separating these long-term survivors (LTS) from short-term survivors (STS) are still insufficiently understood. The purpose of this study was to identify independent prognostic variables for survival by examining molecular profiles of LTS and STS in a clinically well characterized cohort of glioblastoma patients. The cohort consisted of 93 patients diagnosed with primary glioblastoma and treated with radiation therapy plus concomitant and adjuvant chemotherapy as well as bevacizumab administered in the first-line setting or at time of recurrence. Among these, 14 STS (OS ≥ 36 months) were identified, which were all confirmed being IDHwt. For all patients, RNA had previously been purified from microdissected tumor tissue of the diagnostic specimen and analyzed for expression levels by a customized NanoString platform. This covered 800 genes related to glioblastoma cancer hallmarks, including regulation of angiogenesis and immune response. When comparing expression of these genes in LTS vs. STS using a Welsh’s t-test, 14 candidate genes ended up significant (P
Pathoadaptation of a Human Pathogen Through Non-Coding Intergenic Mutations

Most knowledge gained from evolutionary studies of bacteria in natural and experimental settings center around contribution of intragenic mutations on bacterial evolution. While cases of adaptive intergenic mutations have sometimes been reported or explored, none of these studies consider intergenic mutations in a broader context as key players in evolutionary adaptation of bacteria. The focus of this thesis has been to provide novel insights on contributions of non-coding intergenic mutations in natural evolution of bacteria. The model system used for these investigations is adaptation of opportunistic pathogen Pseudomonas aeruginosa in long-term chronic airway infections of Cystic fibrosis (CF) patients. Using sequenced genomes of P. aeruginosa isolated from this setting, 88 intergenic regions under positive selection for adaptive mutations within and across isolates of different P. aeruginosa lineages were identified. Mutations within core promoter are more frequently found than other elements in these intergenic regions and intergenic mutations made a larger numerical contribution to selection of adaptive genes than intragenic. Several genes present within these regions had established roles in CF adaptation of P. aeruginosa and their expressions are altered by the mutation. It was established that mutations upstream ampR increased tolerance of P. aeruginosa to some β-lactam antibiotics.

Mutations in promoter of phuR, encoding receptor of pseudomonas heme uptake system, conferred growth advantage in the presence of hemoglobin demonstrating that P. aeruginosa has adapted towards utilization of iron from hemoglobin. Further investigation of phuR promoter mutation revealed pleiotropic effects on expression of many other genes. The pleiotropic effect by this mutation was contingent on epistatic effects of other mutations in CF adapted genotype of P. aeruginosa. It was also established that this mutation leads increased inhibition of S. aureus and decreased fitness of P. aeruginosa during anoxic growth.

The findings presented in this thesis provide a new dimension for bacterial evolution through intergenic mutations. The knowledge gained here can be applied to future treatment of patients suffering from chronic bacterial infection. Moreover, direct evolution or genetic manipulation of intergenic region offer ample opportunities for better outcomes in biotechnological applications of bacteria.

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Organisations: Department of Biotechnology and Biomedicine, Infection Microbiology
Authors: Khademi, S. M. H. (Intern)
Number of pages: 145
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Peroxyl radical- and photo-oxidation of glucose 6- phosphate dehydrogenase generates cross-links and functional changes via oxidation of tyrosine and tryptophan residues

Protein oxidation is a frequent event as a result of the high abundance of proteins in biological samples and the multiple processes that generate oxidants. The reactions that occur are complex and poorly understood, but can generate major structural and functional changes on proteins. Current data indicate that pathophysiological processes and multiple human diseases are associated with the accumulation of damaged proteins. In this study we investigated the mechanisms and consequences of exposure of the key metabolic enzyme glucose-6-phosphate dehydrogenase (G6PDH) to peroxyl radicals (ROO•) and singlet oxygen (1O2), with particular emphasis on the role of Trp and Tyr residues in protein cross-linking and fragmentation. Cross-links and high molecular mass aggregates were detected by SDS-PAGE and Western blotting using specific antibodies. Amino acid analysis has provided evidence for Trp and Tyr consumption and formation of oxygenated products (diols, peroxides, N-formylkynurenine, kynurenine) from Trp, and di-tyrosine (from Tyr). Mass spectrometric data obtained after trypsin-digestion in the presence of H216O and H218O, has allowed the mapping of specific cross-linked residues and their locations. These data indicate that specific Tyr-Trp and di-Tyr cross-links are formed from residues that are proximal and surface-accessible, and that the extent of Trp oxidation varies markedly between sites. Limited modification at other residues is also detected. These data indicate that Trp and Tyr residues are readily modified by ROO• and 1O2 with this giving products that impact significantly on protein structure and function. The formation of such cross-links may help rationalize the accumulation of damaged proteins in vivo.

General information
Phaeobacter piscinae sp. nov., a species of the Roseobacter group and potential aquaculture probiont

Four heterotrophic, antimicrobial, motile, marine bacterial strains, 27-4T, 8-1, M6-4.2 and S26, were isolated from aquaculture units in Spain, Denmark and Greece. All four strains produced the antibiotic compound tropodithietic acid, which is a key molecule in their antagonism against fish pathogenic bacteria. Cells of the strains were Gram-reaction-negative, rod-shaped and formed star-shaped aggregates in liquid culture and brown-coloured colonies on marine agar. The predominant cellular fatty acids were C18:1ω7c, C16:0, C11 methyl C18:1ω7c and C16:0 2-OH, and the polar lipids comprised phosphatidylglycerol, diphosphatidylglycerol, phosphatidylethanolamine, phosphatidylcholine, an aminolipid, a phospholipid and an unidentified lipid. The strains grew optimally at 31-33°C. Growth was observed at a salt concentration between 0.5 and 5-6% NaCl with an optimum at 2-3%. The pH range for growth of the strains was from pH 6 to 8-8.5 with an optimum at pH 7. Based on 16S rRNA gene sequence analysis, the strains are affiliated with the genus Phaeobacter. The genome sequences of the strains have a DNA G+C content of 60.1% and share an average nucleotide identity (ANI) of more than 95%. The four strains are distinct from the type strains of the closely related species Phaeobacter gallaeciensis and Phaeobacter inhibens based on an ANI of 90.5-91.7% and 89.6-90.4%, respectively, and an in silico DNA-DNA hybridization relatedness of 43.9-46.9% and 39.8-41.9%, respectively. On the basis of phylogenetic analyses as well as phenotypic and chemotaxonomic properties, the isolates are considered to represent a novel species, for which the name Phaeobacter piscinae sp. nov. is proposed. The type strain is 27-4T (=DSM 103509T=LMG 29708T).

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Organisations: Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, DTU Metabolomics Core, Natural Product Discovery, CHEC Research Centre, The Hempel Foundation Coatings Science and Technology Centre (CoaST), Leibniz-Institut DSMZ
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Phosphoribosyl Diphosphate (PRPP): Biosynthesis, Enzymology, Utilization, and Metabolic Significance

Phosphoribosyl diphosphate (PRPP) is an important intermediate in cellular metabolism. PRPP is synthesized by PRPP synthase, as follows: ribose 5-phosphate + ATP → PRPP + AMP. PRPP is ubiquitously found in living organisms and is used in substitution reactions with the formation of glycosidic bonds. PRPP is utilized in the biosynthesis of purine and pyrimidine nucleotides, the amino acids histidine and tryptophan, the cofactors NAD and tetrahydromethanopterin, arabinosyl monophosphodecaprenol, and certain aminoglycoside antibiotics. The participation of PRPP in each of these metabolic pathways is reviewed. Central to the metabolism of PRPP is PRPP synthase, which has been studied from all kingdoms of life by classical mechanistic procedures. The results of these analyses are unified with recent progress in molecular enzymology and the elucidation of the three-dimensional structures of PRPP synthases from eubacteria, archaea, and humans. The structures and mechanisms of catalysis of the five diphosphoryltransferases are compared, as are those of selected enzymes of diphosphoryl transfer, phosphoryl transfer, and nucleotidyl transfer reactions. PRPP is used as a substrate by a large number of phosphoribosyltransferases. The protein structures and reaction mechanisms of these phosphoribosyltransferases vary and demonstrate the versatility of PRPP as an intermediate in cellular physiology. PRPP synthases appear to have originated from a phosphoribosyltransferase during evolution, as demonstrated by phylogenetic analysis. PRPP, furthermore, is an effector molecule of purine and pyrimidine nucleotide biosynthesis, either by binding to PurR or PyrR regulatory proteins or as an allosteric activator of carbamoylphosphate synthetase. Genetic analyses have disclosed a number of mutants altered in the PRPP synthase-specifying genes in humans as well as bacterial species.

General information
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Organisations: Metabolic Signaling and Regulation, Department of Biotechnology and Biomedicine, Technical University of Denmark, Aarhus University, University of Illinois at Urbana-Champaign, University of Copenhagen
Phylogenetic analysis of Monascus and new species from honey, pollen and nests of stingless bees

The genus Monascus was described by van Tieghem (1884) to accommodate M. ruber and M. mucoroides, two species with non-ostiolate ascomata. Species delimitation in the genus is still mainly based on phenotypic characters, and taxonomic studies that include sequence data are limited. The genus is of economic importance. Species are used in fermented Asian foods as food colourants (e.g. ‘red rice’ (ang-kak, angka)) and found as spoilage organisms, and recently Monascus was found to be essential in the lifecycle of stingless bees. In this study, a polyphasic approach was applied combining morphological characters, ITS, LSU, β-tubulin, calmodulin and RNA polymerase II second largest subunit sequences and extrolite data, to delimit species and to study phylogenetic relationships in Monascus. Furthermore, 30 Monascus isolates from honey, pollen and nests of stingless bees in Brazil were included. Based on this polyphasic approach, the genus Monascus is resolved in nine species, including three new species associated with stingless bees (M. flavipigmentosus sp. nov., M. mellicola sp. nov., M. recifensis sp. nov., M. argentensis, M. floridanus, M. lunisporas, M. pallens, M. purpureus, M. ruber), and split in two new sections (section Floridani sect. nov., section Rubri sect. nov.). Phylogenetic analysis showed that the xerophile Monascus eremophilus does not belong in Monascus and monophyly in Monascus is restored with the transfer of M. eremophilus to Penicillium (P. eremophilum comb. nov.). A list of accepted and excluded Monascus and Basipetospora species is given, together with information on (ex-)types cultures and barcode sequence data.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Universidade Federal de Pernambuco, Swedish University of Agricultural Sciences, Westerdijk Fungal Biodiversity Institute
Authors: Barbosa, R. N. (Ekstern), Leong, S. L. (Ekstern), Vinnere-Pettersson, O. (Ekstern), Chen, A. J. (Ekstern), Souza-Motta, C. M. (Ekstern), Frisvad, J. C. (Intern), Samson, R. A. (Ekstern), Oliveira, N. T. (Ekstern), Houbraken, J. (Ekstern)
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ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
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Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Phylogeny of xerophilic aspergilli (subgenus Aspergillus) and taxonomic revision of section Restricti
Aspergilli section Restricti together with sister section Aspergillus (formerly Eurotium) comprises xerophilic species, that are able to grow on substrates with low water activity and in extreme environments. We addressed the monophyly of both sections within subgenus Aspergillus and applied a multidisciplinary approach for definition of species boundaries in sect. Restricti. The monophyly of sections Aspergillus and Restricti was tested on a set of 102 isolates comprising all currently accepted species and was strongly supported by Maximum likelihood (ML) and Bayesian inference (BI) analysis based on β-tubulin (benA), calmodulin (CaM) and RNA polymerase II second largest subunit (RPB2) loci. More than 300 strains belonging to sect. Restricti from various isolation sources and four continents were characterized by DNA sequencing, and 193 isolates were selected for phylogenetic analyses and phenotypic studies. Species delimitation methods based on multispecies coalescent model were employed on DNA sequences from four loci, i.e., ID region of rDNA (ITS + 28S), CaM, benA and RPB2, and supported recognition of 21 species, including 14 new. All these species were also strongly supported in ML and BI analyses. All recognised species can be reliably identified by all four examined genetic loci. Phenotype analysis was performed to support the delimitation of new species and includes colony characteristics on seven cultivation media incubated at several temperatures, growth on an osmotic gradient (six media with NaCl concentration from 0 to 25 %) and analysis of morphology including scanning electron microscopy. The micromorphology of conidial heads, vesicle dimensions, temperature profiles and growth parameters in osmotic gradient were useful criteria for species identification.

The vast majority of species in sect. Restricti produce asperglaucide, asperphenamate or both in contrast to species in sect. Aspergillus. Mycophenolic acid was detected for the first time in at least six members of the section. The ascomata of A. halophilicus do not contain auroglaucin, epiheveadride or flavoglaucin which are common in sect. Aspergillus, but shares the echinulins with sect. Aspergillus.

General information
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Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Charles University, EMSL Analytical, Inc., University of Ljubljana, University of Ottawa, Westerdijk Fungal Biodiversity Institute, Université de Brest, National Center for Agricultural Utilization Research
Pages: 161-236
Physiological characterization of secondary metabolite producing Penicillium cell factories

Penicillium species are important producers of bioactive secondary metabolites. However, the immense diversity of the fungal kingdom is only scarcely represented in industrial bioprocesses and the upscaling of compound production remains a costly and labor intensive challenge. In order to facilitate the development of novel secondary metabolite producing processes, two routes are typically explored: optimization of the native producer or transferring the enzymatic pathway into a heterologous host. Recent genome sequencing of ten Penicillium species showed the vast amount of secondary metabolite gene clusters present in their genomes, and makes them accessible for rational strain improvement. In this study, we aimed to characterize the potential of these ten Penicillium species as native producing cell factories by testing their growth performance and secondary metabolite production in submerged cultivations. Cultivation of the fungal species in controlled submerged bioreactors showed that the ten wild type Penicillium species had promising, highly reproducible growth characteristics in two different media. Analysis of the secondary metabolite production using liquid chromatography coupled with high resolution mass spectrometry proved that the species produced a broad range of secondary metabolites, at different stages of the fermentations. Metabolite profiling for identification of the known compounds resulted in identification of 34 metabolites; which included several with bioactive properties such as antibacterial, antifungal and anti-cancer activities. Additionally, several novel species-metabolite relationships were found. This study demonstrates that the fermentation characteristics and the highly reproducible performance in bioreactors of ten recently genome sequenced Penicillium species should be considered as very encouraging for the application of native hosts for production via submerged fermentation. The results are particularly promising for the potential development of the ten analysed Penicillium species for production of novel bioactive compounds via submerged fermentations.

General information
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Organisations: Department of Biotechnology and Biomedicine, Biosynthetic Pathway Engineering, Novo Nordisk Foundation Center for Biosustainability, Yeast Cell Factories, Natural Product Discovery, Fungal Chemodiversity, DTU Metabolomics Core, Department of Systems Biology, Fungal Physiology and Biotechnology, Chalmers University of Technology
Authors: Grijseels, S. (Intern), Nielsen, J. (Ekstern), Nielsen, J. (Intern), Larsen, T. O. (Intern), Frisvad, J. C. (Intern), Nielsen, K. F. (Intern), Frandsen, R. J. N. (Intern), Workman, M. (Intern)
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Pitfalls to avoid when using phage display for snake toxins

Antivenoms against bites and stings from snakes, spiders, and scorpions are associated with immunological side effects and high cost of production, since these therapies are still derived from the serum of hyper-immunized production animals. Biotechnological innovations within envenoming therapies are thus warranted, and phage display technology may be a promising avenue for bringing antivenoms into the modern era of biologics. Although phage display technology represents a robust and high-throughput approach for the discovery of antibody-based antitoxins, several pitfalls may present themselves when animal toxins are used as targets for phage display selection. Here, we report selected critical challenges from our own phage display experiments associated with biotinylation of antigens, clone picking, and the presence of amber codons within antibody fragment structures in some phage display libraries. These challenges may be detrimental to the outcome of phage display experiments, and we aim to help other researchers avoiding these pitfalls by presenting their solutions.

General information
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Organisations: Network Engineering of Eukaryotic Cell factories, Department of Biotechnology and Biomedicine, Universidad de Costa Rica, University of Copenhagen
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Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 2.33 SJR 0.766 SNIP 1.047
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Scopus rating (2012): SJR 1.019 SNIP 1.346 CiteScore 2.85
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ISI indexed (2011): ISI indexed yes
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Scopus rating (2010): SJR 0.872 SNIP 1.138
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.756 SNIP 0.974
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.898 SNIP 1.056
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.828 SNIP 1.108
Scopus rating (2006): SJR 1.115 SNIP 1.078
Molecular characterization of plant cell wall glycosyltransferases is a critical step towards understanding the biosynthesis of the complex plant cell wall, and ultimately for efficient engineering of biofuel and agricultural crops. The majority of these enzymes have proven very difficult to obtain in the needed amount and purity for such molecular studies, and recombinant cell wall glycosyltransferase production efforts have largely failed. A daunting number of strategies can be employed to overcome this challenge, including optimization of DNA and protein sequences, choice of expression organism, expression conditions, co-expression partners, purification methods, and optimization of protein solubility and stability. Hence researchers are presented with thousands of potential conditions to test. Ultimately, the subset of conditions that will be sampled depends on practical considerations and prior knowledge of the enzyme(s) being studied.

We have developed a rational approach to this process. We devise a pipeline comprising in silico selection of targets and construct design, and high-throughput expression screening, target enrichment, and hit identification. We have applied this pipeline to a test set of Arabidopsis thaliana cell wall glycosyltransferases known to be challenging to obtain in soluble form, as well as to a library of cell wall glycosyltransferases from other plants including agricultural and biofuel crops. The screening results suggest that recombinant cell wall glycosyltransferases in general have a very low soluble: insoluble ratio in lysates from heterologous expression cultures, and that co-expression of chaperones as well as lysis buffer optimization can increase this ratio. We have applied the identified preferred conditions to Reversibly Glycosylated Polypeptide 1 from Arabidopsis thaliana, and processed this enzyme to near-purity in unprecedented milligram amounts. The obtained preparation of Reversibly Glycosylated Polypeptide 1 has the expected arabinopyranose mutase and autoglycosylation activities.

**General information**

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Organisations: Department of Biotechnology and Biomedicine, Novo Nordisk Foundation Center for Biosustainability, Enzyme Engineering & Structural Biology
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Plant Polyphenols Stimulate Adhesion to Intestinal Mucosa and Induce Proteome Changes in the Probiotic Lactobacillus acidophilus NCFM

Scope: Plant phenolics, known to exert beneficial effects on human health, were supplemented to cultures of the probiotic bacterium Lactobacillus acidophilus NCFM (NCFM) to assess their effect on its adhesive capacity and the abundancy of individual proteins.

Methods and results: The presence of resveratrol and ferulic acid during bacterial growth stimulated adhesion of NCFM to mucin and human intestinal HT-29 cells, while tannic acid improved adhesion only to HT-29 cells and caffeic acid had very modest effect overall. Some dosage dependence was found for the four phenolics supplemented at 100, 250 or 500
μg/mL to the cultures. Notably, 500 μg/mL ferulic acid only stimulated adhesion to mucin. Analyses of differential whole-cell as well as surface proteomes revealed relative abundance changes for a total of 27 and 22 NCFM proteins, respectively. These changes include enzymes acting in metabolic pathways, such as glycolysis, nucleotide metabolism and stress response as well as being known moonlighting or surface-associated proteins.

Conclusion: The five plant phenolics found in various foods stimulate the adhesive capacity of NCFM in diverse ways and elicited relative abundance changes of specific proteins providing molecular level insight into the mechanism of the putative beneficial effects of the polyphenols.

General information
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Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Disease Systems Immunology, University of Turin, Technical University of Denmark
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Web of Science (2017): Indexed Yes
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Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 1.702 SNIP 1.404 CiteScore 4.53
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.687 SNIP 1.439 CiteScore 4.55
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 1.681 SNIP 1.485 CiteScore 4.92
ISI indexed (2013): ISI indexed yes
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Scopus rating (2011): SJR 1.533 SNIP 1.495 CiteScore 4.54
ISI indexed (2011): ISI indexed yes
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BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.568 SNIP 1.542
BFI (2009): BFI-level 1
Web of Science (2009): Indexed yes
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Scopus rating (2008): SJR 1.183 SNIP 1.234
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.024 SNIP 1.214
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.638 SNIP 0.726
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.315 SNIP 0.539
Polyphasic taxonomy of Aspergillus section Aspergillus (formerly Eurotium), and its occurrence in indoor environments and food

Aspergillus section Aspergillus (formerly the genus Eurotium) includes xerophilic species with uniseriate conidiophores, globose to subglobose vesicles, green conidia and yellow, thin walled eurotium-like ascomata with hyaline, lenticular ascospores. In the present study, a polyphasic approach using morphological characters, extrolites, physiological characters and phylogeny was applied to investigate the taxonomy of this section. Over 500 strains from various culture collections and new isolates obtained from indoor environments and a wide range of substrates all over the world were identified using calmodulin gene sequencing. Of these, 163 isolates were subjected to molecular phylogenetic analyses using sequences of ITS rDNA, partial β-tubulin (BenA), calmodulin (CaM) and RNA polymerase II second largest subunit (RPB2) genes. Colony characteristics were documented on eight cultivation media, growth parameters at three incubation temperatures were recorded and micromorphology was examined using light microscopy as well as scanning electron microscopy to illustrate and characterise each species. Many specific extrolites were extracted and identified from cultures, including echinulins, epiveadrides, auroglaucins and anthraquinone bisanthrons, and to be consistent in strains of nearly all species. Other extrolites are species-specific, and thus valuable for identification. Several extrolites show antioxidant effects, which may be nutritionally beneficial in food and beverages. Important mycotoxins in the strict sense, such as sterigmatocystin, aflatoxins, ochratoxins, citrinin were not detected despite previous reports on their production in this section. Adopting a polyphasic approach, 31 species are recognised, including nine new species. ITS is highly conserved in this section and does not distinguish species. All species can be differentiated using CaM or RPB2 sequences. For BenA, Aspergillus brunneus and A. niveoglaucus share identical sequences. Ascospores and conidia morphology, growth rates at different temperatures are most useful characters for phenotypic species identification.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Chinese Academy of Medical Sciences, University of Ottawa, Westerdijk Fungal Biodiversity Institute, Anadolu University, Charles University, Chinese Academy of Sciences, University of Szeged, EMSL Analytical, Inc.
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Pre-Treatment of Synovial Fluid Enable Precise and Accurate Measurement of Neo-Epitope Biomarkers

General information
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Organisations: DTU Proteomics Core, Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Nordic Bioscience AS, Aalborg University Hospital, University of Surrey
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Profiling bacterial kinase activity using a genetic circuit

Phosphorylation is a post-translational modification that regulates the activity of several key proteins in bacteria and eukaryotes. Accordingly, a variety of tools has been developed to measure kinase activity. To couple phosphorylation to an in vivo fluorescent readout we used the Bacillus subtilis kinase PtkA, transmembrane activator TkmA and the repressor FatR to construct a genetic circuit in E. coli. By tuning the repressor and kinase expression level at the same time, we were able to show a 4.2-fold increase in signal upon kinase induction. We furthermore validated that the previously reported FatR Y45E mutation attenuates operator repression. This genetic circuit provides a starting point for computational protein design and a metagenomic library-screening tool.

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Profiling evolutionary landscapes underlying drug resistance

Bacteria have existed on earth for 3.5 million years and their ability to evolve has allowed for their survival in almost all global niches. Bacteria evolve and adapt easily due to their short generation times, plastic genomes, acquisition (external) DNA and their ability to form protective bacterial communities i.e. biofilms or dormant metabolic states. Antibiotic drugs are currently our best medicine to treat (against) bacterial pathogens due to antibiotics unique properties of being small molecules that are soluble and act systemically. These qualities allow for many modern medical procedures to occur due to antibiotics preventative/ prophylactic and therapeutic qualities. Despite bacterial antibiotic resistance mechanisms always being present in nature, the overuse and misuse of antibiotics by humans are accelerating the rise and dissemination of bacterial antibiotic resistance. Bacterial antibiotic resistance is a global threat to public health; especially because of lack of new drugs. It has been highlighted that understanding antibiotic resistance by further elucidating mechanisms of evolution, molecular mechanisms of action and reservoirs of resistance are essential Therefore, the work involved in this PhD thesis, examines the evolution of antibiotic resistance in bacterial populations.

Two main studies were performed: the first to elucidate the molecular mechanisms of collateral sensitive drug pairs and collateral resistance drug pairs in adaptation of Escherichia coli populations; and the second exploring mutant variant dynamics in cystic fibrosis lung, by analyzing sputum samples from chronic carriers of Pseudomonas aeruginosa undergoing antibiotic treatment.

Both studies explore the trajectories of antibiotic resistance within bacterial populations: the first study by exploring antibiotic resistance loci, and the in the second by whole-gene sequencing. The desired outcome from both studies is to find methods to use antibiotic therapy more rationally to treat infection efficiently and effectively whilst reducing the evolution of antibiotic resistance.

Protein Sorting Prediction

Many computational methods are available for predicting protein sorting in bacteria. When comparing them, it is important to know that they can be grouped into three fundamentally different approaches: signal-based, global-property-based and homology-based prediction. In this chapter, the strengths and drawbacks of each of these approaches is described through many examples of methods that predict secretion, integration into membranes, or subcellular locations in general. The aim of this chapter is to provide a user-level introduction to the field with a minimum of computational theory.
Proteomic approaches for quantitative cancer cell signaling

Cancer is a genetic disease and historically the discovery of underlying genetic alterations has been critical to our understanding of disease and past treatment successes. However, cancer still poses an important health threat and most available drugs are not capable of providing complete remission. Drug targets are typically proteins, but are based on genetic findings. Thus studying cancer systems at the level of proteins and their signaling can provide the additional level of data needed for the development of effective drugs. This thesis summarizes the work undertaken during my doctoral studies in an effort to contribute to the study of signaling dynamics in cancer systems. This thesis is divided into two parts. Part I begins with a brief introduction in the use of omics in systems cancer research with a focus on mass spectrometry as a means to quantitatively measure protein and signaling dynamics in the identified protein networks (Chapter 1). Gene fusions are portrayed in-depth as an example of a major genetic alteration found to occur in a variety of cancers, the most infamous of which has lead to the development of the specific tyrosine kinase inhibitor imatinib and a major success in the treatment of chronic myelogenous leukemia. However, this is the exception rather than the norm as most drugs are developed based on genetic findings while designed to act on the protein level, and might contribute to explaining the paucity of specific effective cancer therapeutics available. Furthermore, this underlines the importance of proteomic studies and the conclusions drawn for the high-throughput data generated in the latter. Chapter 2 gives a temporal overview of precision gene-editing in the context of systems biology. Following the past successes of methods such as zinc-finger nuclease and TALEs, the novel CRISPR-Cas technology has rapidly become an extremely popular gene-editing tool. Its mechanism of action, several applications and potential shortcomings are discussed. The Chapter is concluded with a final application: chromosomal translocations can be generated in vitro or in vivo using nuclease-based targeted gene editing. Part II illustrates the use of mass spectrometry-based proteomics and phospho-proteomics in studying the effects of perturbations at the cellular level. Chapter three captures the very early signaling dynamics related to cell migration following wounding in triple negative breast cancer cells, and their potential role as novel targets for therapies aimed at reducing the metastases. Chapter four describes the induction of the oncogenic chimeric gene PRKAR1A-RET in thyroid cells. Its transformative potential is shown and the ensuing changes are measured at the protein and signaling levels. This study demonstrates the use of the novel CRISPR-Cas technology for the generation of chromosomal rearrangements in vitro and investigates the effects of this important genetic aberration in a physiologically relevant cellular setting. Part III concludes the thesis by providing a global discussion and future perspectives for the studies presented in part II. Overall, the work presented herein aims to underscore the importance of studying cancer systems at the protein level, the dynamics of which define phenotypic outcome. The effects of cellular and genetic perturbations at the protein network level were studied using mass spectrometry-based proteomics and, the results whereof suggest interesting avenues for future development of cancer therapies.
Pseudochelin A, a siderophore of Pseudoalteromonas piscicida S2040
A new siderophore containing a 4,5-dihydroimidazole moiety was isolated from Pseudoalteromonas piscicida S2040 together with myxochelins A and B, alteramide A and its cycloaddition product, and bromo- and dibromoalterochromides. The structure of pseudochelin A was established by spectroscopic techniques including 2D NMR and MS/MS fragmentation data. In bioassays selected fractions of the crude extract of S2040 inhibited the opportunistic pathogen Pseudomonas aeruginosa. Pseudochelin A displayed siderophore activity in the chrome azurol S assay at concentrations higher than 50 μM, and showed weak activity against the fungus Aspergillus fumigatus, but did not display antibacterial, anti-inflammatory or anticonvulsant activity.
Lack of access to certain types of oligosaccharides is a severe bottleneck for advances in glycosciences. The transglycosylation activity of retaining glycoside hydrolases (GH) has been used to provide oligosaccharides. The main drawbacks of those enzymes are the competing hydrolysis reaction and the fact that the products are also substrates, thus needing a kinetic control of the reaction. Several approaches have been developed to overcome these, including mechanism modifications (e.g. glycosynthases, chemical rescue), functional screening and data mining to find natural transglycosidases, directed evolution and targeted mutagenesis. Here we focused on N-acetyl hexosaminidases from family GH20 that catalyse removal or addition of GlcNAc and GalNAc. Despite sharing a substrate-assisted mechanism with GH85, for which several glycosynthases have been created, no successful GH20 glycosynthase has been reported. Thus, we turned to discovery and characterization of new GH20s and performing a systematic mutagenesis study. Several new GH20s of bacterial origin were isolated and described by functional screening and data mining, including transglycosidases able to synthesize lacto-N-triose, a valuable oligosaccharide, as well as genuine hydrolases. Mutational analysis of all residues within the catalytic domain which were unchanged in >99% of 371 aligned GH20 sequences was pursued. Indeed, it has been shown that targeting conserved residues increases the likelihood of finding advantageous mutations. Furthermore, it allows for transfer of successful mutations to other GH20s to find new efficient transglycosidases. Notably, even though most conserved residues occur within the first and second shell of substrate interaction, 9 residues inside the (β/α)8 barrel pointing toward the active site are also conserved. To the best of our knowledge, such residues were not studied, although one of them mutated by directed evolution of a GH29 enzyme improved the transglycosylation yield and was transferable to other GH29 members. Here transglycosylation yields of mutants in first shell, second shell and other residues within the (β/α)8 barrel will be compared for GH20.

General information
State: Published
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RAIN: RNA-protein Association and Interaction Networks

Protein association networks can be inferred from a range of resources including experimental data, literature mining and computational predictions. These types of evidence are emerging for non-coding RNAs (ncRNAs) as well. However, integration of ncRNAs into protein association networks is challenging due to data heterogeneity. Here, we present a database of ncRNA-RNA and ncRNA-protein interactions and its integration with the STRING database of protein-protein interactions. These ncRNA associations cover four organisms and have been established from curated examples, experimental data, interaction predictions and automatic literature mining. RAIN uses an integrative scoring scheme to assign a confidence score to each interaction. We demonstrate that RAIN outperforms the underlying microRNA-target predictions in inferring ncRNA interactions. RAIN can be operated through an easily accessible web interface and all interaction data can be downloaded.

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Web of Science (2016): Indexed yes
Scopus rating (2015): SJR 1.491 SNIP 0.905 CiteScore 2.21
Web of Science (2015): Indexed yes
Scopus rating (2014): SJR 1.915 SNIP 1.109 CiteScore 2.75
Scopus rating (2013): SJR 2.28 SNIP 1.721 CiteScore 3.66
Scopus rating (2012): SJR 2.03 SNIP 0.984 CiteScore 3.35
Scopus rating (2011): SJR 1.466 SNIP 0.758 CiteScore 2.5
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Recombinant snakebite antivenoms: A cost-competitive solution to a neglected tropical disease?

Snakebite envenoming is a major public health burden in tropical parts of the developing world. In sub-Saharan Africa, neglect has led to a scarcity of antivenoms threatening the lives and limbs of snakebite victims. Technological advances within antivenom are warranted, but should be evaluated not only on their possible therapeutic impact, but also on their cost-competitiveness. Recombinant antivenoms based on oligoclonal mixtures of human IgG antibodies produced by CHO
cell cultivation may be the key to obtaining better snakebite envenoming therapies. Based on industry data, the cost of treatment for a snakebite envenoming with a recombinant antivenom is estimated to be in the range USD 60-250 for the Final Drug Product. One of the effective antivenoms (SAIMR Snake Polyvalent Antivenom from the South African Vaccine Producers) currently on the market has been reported to have a wholesale price of USD 640 per treatment for an average snakebite. Recombinant antivenoms may therefore in the future be a cost-competitive alternative to existing serum-based antivenoms.

General information
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BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.97
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 4.09
Scopus rating (2014): CiteScore 4.61
Scopus rating (2013): CiteScore 4.72
ISI indexed (2013): ISI indexed yes
Scopus rating (2012): CiteScore 4.75
ISI indexed (2012): ISI indexed yes
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ISI indexed (2011): ISI indexed no
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Reconstruction of the metabolic network of Pseudomonas aeruginosa to interrogate virulence factor synthesis
Virulence-linked pathways in opportunistic pathogens are putative therapeutic targets that may be associated with less potential for resistance than targets in growth-essential pathways. However, efficacy of virulence-linked targets may be affected by the contribution of virulence-related genes to metabolism. We evaluate the complex interrelationships between growth and virulence-linked pathways using a genome-scale metabolic network reconstruction of Pseudomonas aeruginosa strain PA14 and an updated, expanded reconstruction of P. aeruginosa strain PAO1. The PA14 reconstruction accounts for the activity of 112 virulence-linked genes and virulence factor synthesis pathways that produce 17 unique compounds. We integrate eight published genome-scale mutant screens to validate gene essentiality predictions in rich media, contextualize intra-screen discrepancies and evaluate virulence-linked gene distribution across essentiality datasets. Computational screening further elucidates interconnectivity between inhibition of virulence factor synthesis and growth. Successful validation of selected gene perturbations using PA14 transposon mutants demonstrates the utility of model-driven screening of therapeutic targets.
Reprogramming amino acid catabolism in CHO cells with CRISPR-Cas9 genome editing improves cell growth and reduces by-product secretion

CHO cells primarily utilize amino acids for three processes: biomass synthesis, recombinant protein production and catabolism. In this work, we disrupted 9 amino acid catabolic genes participating in 7 different catabolic pathways, to increase synthesis of biomass and recombinant protein, while reducing production of growth-inhibiting metabolic by-products from amino acid catabolism.
Response to Pitt and Taylor 2016: Conservation of Aspergillus with A. niger as the conserved type is unnecessary and potentially disruptive

Aspergillus is a diverse fungal genus containing many species of great agricultural, biotechnological and medical relevance. Because of the broad use of the genus name in diverse disciplines, and the importance of individual species names in these areas, the taxonomy and nomenclature of Aspergillus should remain stable. A formal proposal to change the generic type from A. glaucus to A. niger was recently published. Here we present arguments against this proposal. We assert that it should be rejected because it will not ensure nomenclatural stability for Aspergillus, and will put the names of several important species, such as A. flavus, A. fumigatus and A. oryzae at risk of being classified in different genera and being lost.

General information
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Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Westerdijk Fungal Biodiversity Institute, Erasmus MC University Medical Center, National Research Council of Italy, University of Ottawa, University of Szeged, USDA-ARS, Charles University, Korean Agricultural Culture Collection, Agriculture and Agri-Food Canada, Chiba University
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 1.17 SJR 0.974 SNIP 1.531
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Scopus rating (2015): SJR 1.023 SNIP 1.699 CiteScore 1.38
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 1.147 SNIP 2.084 CiteScore 1.67
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 0.866 SNIP 1.878 CiteScore 1.58
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 0.945 SNIP 1.456 CiteScore 1.5
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Revealing the compact structure of lactic acid bacterial hetero-exopolysaccharides by SAXS and DLS

Molecular structures of exopolysaccharides are required to understand their functions and the relationships between the structure and physical and rheological properties. Small-angle X-ray scattering and dynamic light scattering were used in conjunction with molecular modeling to characterize solution structures of three lactic acid bacterial hetero-exopolysaccharides (HePS-1, HePS-2 and HePS-3). Values of radius of gyration \( R_G \), cross-sectional radius of gyration \( R_{XS} \), approximate length \( L \) and hydrodynamic diameter were not directly proportional to the molar mass and indicated the HePSs adopted a compact coil-like rather than an extended conformation. Constrained molecular modeling of 15,000 randomised HePS-1 conformers resulted in five best-fit structures with R factor of 3.94.6% revealing random coil-like structure. \( \Phi \) and \( \Psi \) angle analysis of glycosidic linkages in HePS-1 structures suggests Galf residues significantly influence the conformation. Ab initio scattering modeling of HePS-2 and HePS-3 gave excellent curve fittings with \( \chi^2 \) of 0.43 and 0.34 for best-fit models, respectively, compatible with coil-like conformation. The findings disclose solution behaviour of HePS relevant for their interactions with biomacromolecules e.g. milk proteins.
Ribosome profiling-guided depletion of an mRNA increases cell growth rate and protein secretion

Recombinant protein production coopts the host cell machinery to provide high protein yields of industrial enzymes or biotherapeutics. However, since protein translation is energetically expensive and tightly controlled, it is unclear if highly expressed recombinant genes are translated as efficiently as host genes. Furthermore, it is unclear how the high expression impacts global translation. Here, we present the first genome-wide view of protein translation in an IgG-producing CHO cell line, measured with ribosome profiling. Through this we found that our recombinant mRNAs were translated as efficiently as the host cell transcriptome, and sequestered up to 15% of the total ribosome occupancy. During cell culture, changes in recombinant mRNA translation were consistent with changes in transcription, demonstrating that transcript levels influence specific productivity. Using this information, we identified the unnecessary resistance marker NeoR to be a highly transcribed and translated gene. Through siRNA knock-down of NeoR, we improved the production- and growth capacity of the host cell. Thus, ribosomal profiling provides valuable insights into translation in CHO cells and can guide efforts to enhance protein production.

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Risk factors and predictors of dementia and cognitive impairment

The greying of the world population has led to what was previously referred to as the "silent" epidemic of our century, namely dementia. The epidemic is primarily driven by an epidemiological transition, where prolonged longevity and declining fertility rates have led to increasing proportions of older people in the total population. Dementia and cognitive impairment are by far the leading causes of disability and in particularly the need for care among older people. Surprisingly there has been much less investment in dementia research, given its burden.

Consequently, Alzheimer's disease, being the most prevalent dementia type, is the only cause of death among the top 10 killers in the United States that cannot be prevented, cured, or even delayed. The knowledge of risk and protective factors is therefore especially important for the development of prevention strategies, as prevention by risk factor intervention, is considered the key to a better control of the epidemic. Women outlive men on average, however they have poorer health status. Moreover, women have an elevated risk of dementia. This clearly justifies an increased focus on dementia specifically for women. In the development of new disease modifying interventions there has been a devastating low rate of success in the area of dementia. Resources have therefore been directed at identifying preclinical stages of dementia-related diseases as this is considered the optimal "window" for intervention. Identification of subjects with preclinical disease and subsequent high likelihood of progression are therefore an indisputable prerequisite for the success of future drugs. Here, biomarkers play a crucial role, as the pre-symptomatic diagnosis will rely on these. Hence, advances in biomarkers, especially non-invasive blood-based biomarkers, are required to ensure that the new drugs are tested on the right patients at the right time.

The aims of this thesis were: i) to identify risk factors for all cause and differential dementia diagnoses, ii) to identify risk factors associated with progression from normal cognition to dementia within the follow-up period and iii) to evaluate the possible utility of two novel serological biomarkers of truncated tau as predictors of incident dementia. This was investigated using data from the Prospective Epidemiological Risk Factor (PERF) study, a population-based prospective cohort study on 5,855 elderly Danish women initially enrolled between year 1999 and 2001 with a follow-up examination of 2,103 of the women in year 2013-2014.

We aimed at identifying risk factors for incident dementia and its subtypes in chapter 4. With special focus on a range of metabolic risk factors we investigated how these factors were related to cognitive dysfunction at the follow-up visit (chapter 5). These studies found that Body Mass Index (BMI) in the overweight range and physical activity were associated with lower risk of dementia (Chapter 4), while increasing age, history of depression, insulin resistance (using the homeostasis model assessment index) and elevated fasting plasma glucose increased the risk of dementia or cognitive dysfunction (chapter 4 or Chapter 5, respectively).

In chapter 6 we specifically aimed at assessing the risk of progression to dementia in subpopulation(s) of women with signs of mild cognitive deficits and further to investigate the cognitive courses from baseline to follow-up (reverse trajectory, stable, and progressive) including a risk-profile specifically associated with progression. We found that the degree of cognitive impairment at baseline (single versus multiple domains) was an important predictor of dementia and in subjects with subtle objective cognitive impairment physical inactivity, elevated total cholesterol and a history of depression were associated with progression to dementia or severe cognitive impairment.

In chapter 7, we evaluated the possible utility of two novel serological biomarkers of truncated tau as predictors of incident dementia in women. We found that high levels of Tau-A and Tau-C were associated with lower risk of dementia and Alzheimer's disease. Tau-C gave a very modest increase in the area under the curve (AUC) in a 5-year prediction horizon as compared to a reference model with age and education.

Finally, we summarised our results in a nomogram, a simple tool for prediction of dementia tailored for individual risk prediction. This illustrates the applicability of such findings for dementia risk screening (chapter 8). Overall, many of the identified risk factors are considered modifiable and therefore provide further evidence that prevention strategies could be a way to counteract the otherwise poor future prospects for dementias in the ageing population. Also, we show that the risk factors and blood-based tau biomarkers may be useful in screening and thereby early identification of individuals at-risk for dementia, one of the most persisting needs in dementia drug development.

General information

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Selection of Bacillus species for targeted in situ release of prebiotic galacto-rhamnogalacturonan from potato pulp in piglets

We have previously shown that galacto-rhamnogalacturonan fibers can be enzymatically extracted from potato pulp and that these fibers have potential for exerting a prebiotic effect in piglets. The spore-forming Bacillus species are widely used as probiotics in feed supplements for pigs. In this study, we evaluated the option for further functionalizing Bacillus feed supplements by selecting strains possessing the enzymes required for extraction of the potentially prebiotic fibers. We established that it would require production and secretion of pectin lyase and/or polygalacturonase but no or limited secretion of galactanase and β-galactosidase. By screening a library of 158 Bacillus species isolated from feces and soil, we demonstrated that especially strains of Bacillus amyloliquefaciens, Bacillus subtilis, and Bacillus mojavensis have the necessary enzyme profile and thus the capability to degrade polygalacturonan. Using an in vitro porcine gastrointestinal model system, we revealed that specifically strains of B. mojavensis were able to efficiently release galacto-rhamnogalacturonan from potato pulp under simulated gastrointestinal conditions. The work thus demonstrated the feasibility of producing prebiotic fibers via a feed containing Bacillus spores and potato pulp and identified candidates for future in vivo evaluation in piglets.
Pseudomonas aeruginosa is the primary cause of chronic airway infections in cystic fibrosis (CF) patients. Persistent infections are seen from the first P. aeruginosa culture in about 75% of young CF patients, and it is important to discover new ways to detect P. aeruginosa at an earlier stage. The P. aeruginosa biomarker hydrogen cyanide (HCN) contains a triple bond, which is utilized in this study because of the resulting characteristic C≡N peak at 2135 cm⁻¹ in a Raman spectrum. The Raman signal was enhanced by surface-enhanced Raman spectroscopy (SERS) on a Au-coated SERS substrate. After long-term infection, a mutation in the patho-adaptive lasR gene can alter the expression of HCN, which is why it is sometimes not possible to detect HCN in the breath of chronically infected patients. Four P. aeruginosa reference strains and 12 clinical P. aeruginosa strains isolated from CF children were evaluated, and HCN was clearly detected from overnight cultures of all wild type-like isolates and half of the later isolates from the same patients. The clinical impact could be that P. aeruginosa infections could be detected at an earlier stage, because daily breath sampling with an immediate output could be possible with a point-of-care SERS device.
Shared genetic variants suggest common pathways in allergy and autoimmune diseases

Background: The relationship between allergy and autoimmune disorders is complex and poorly understood.

Objective: To investigate commonalities in genetic loci and pathways between allergy and autoimmune diseases to elucidate shared disease mechanisms.

Methods: We meta-analyzed two GWAS on self-reported allergy and sensitization comprising a total of 62,330 individuals. These results were used to calculate enrichment for SNPs previously associated with autoimmune diseases. Furthermore, we probed for enrichment within genetic pathways and of transcription factor binding sites, and characterized commonalities in the variant burden on tissue-specific regulatory sites by calculating the enrichment of allergy SNPs falling
in gene regulatory regions in various cells using Encode Roadmap DHS data, and compared the allergy data with all known diseases.

Conclusion: Among 290 loci previously associated with 16 autoimmune diseases, we found a significant enrichment of loci also associated with allergy (p=1.4e-17) encompassing 29 loci at a false discovery rate

**General information**

State: Published  
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Systems Biology, University of Copenhagen, Helmholtz Zentrum Muenchen German Research Center for Environmental Health, Boston Children’s Hospital, Broad Institute of Harvard University and Massachusetts Institute of Technology, Imperial College London, University of Queensland, University of Western Australia, University of Groningen, Harvard Medical School, Sir Charles Gairdner Hospital, University Hospital of South Manchester NHS Foundation Trust, 23andMe, University of Manchester, University of Bristol, Queensland Institute of Medical Research, University of London  
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Scopus rating (2009): SJR 3.915 SNIP 2.48  
BFI (2008): BFI-level 2  
Scopus rating (2008): SJR 4.146 SNIP 2.388
Sprifermin (rhFGF18) modulates extracellular matrix turnover in cartilage explants ex vivo

Background: Sprifermin (recombinant human fibroblast growth factor 18) is in clinical development as a potential disease-modifying osteoarthritis drug (DMOAD). In vitro studies have shown that cartilage regenerative properties of sprifermin involve chondrocyte proliferation and extracellular matrix (ECM) production. To gain further insight into the process of sprifermin in the cartilage tissue, this study aimed at investigating the ECM turnover of articular cartilage explants in a longitudinal manner.

Methods: Bovine full-depth articular cartilage explants were stimulated with sprifermin or placebo at weekly intervals, similar to the dosing regimen used in clinical trials. Pre-culturing with oncostatin M and tumour necrosis factor-a, was also used to induce an inflammatory state before treatment. Metabolic activity was measured using AlamarBlue, and chondrocyte proliferation was visualized by immuno-histochemical detection of proliferating cell nuclear antigen. ECM turnover was quantified by biomarker ELISAs; ProC2 reflecting type II collagen formation, CS846 reflecting aggrecan formation, active MMP9, C2M and AGNx2 reflecting matrix metalloproteinase activity, and AGNx1 reflecting aggrecanase activity.

Results: Sprifermin was able to reach the chondrocytes through the extracellular matrix, as it increased cell proliferation and metabolic activity of explants. ProC2 and CS846 was dose-dependently increased (P <0.05) by sprifermin compared to placebo, while C2M and AGNx2 were unaffected, active MMP9 was slightly decreased, and AGNx1 was slightly increased. Over the course of treatment, the temporal order of ECM turnover responses was AGNx1, then ProC2, followed by CS846 and MMP9. Pro-inflammatory activation of the explants diminished the ECM turnover responses otherwise observed under non-inflammatory conditions. Conclusions: The data suggest that sprifermin has chondrogenic effects on articular cartilage ex vivo, exerted through a sequential process of ECM turnover; aggrecan degradation seems to occur first, while type II collagen and aggrecan production increased at a later time point. In addition, it was observed that these chondrogenic effects are dependent on the inflammatory status of the cartilage prior to treatment.
Stable production of the antimalarial drug artemisinin in the moss Physcomitrella patens

Malaria is a real and constant danger to nearly half of the world’s population of 7.4 billion people. In 2015, 212 million cases were reported along with 429,000 estimated deaths. The World Health Organization recommends Artemisinin-based Combinatorial Therapies (ACTs), and the artemisinin for this purpose is mainly isolated from the plant Artemisia annua. However, the plant supply of artemisinin is irregular, leading to fluctuation in prices. Here we report the development of a simple, sustainable, and scalable production platform of artemisinin. The five genes involved in artemisinin biosynthesis were engineered into the moss Physcomitrella patens via direct in vivo assembly of multiple DNA
fragments. In vivo biosynthesis of artemisinin was obtained without further modifications. A high initial production of 0.21 mg/g dry weight artemisinin was observed after only three days of cultivation. Our study shows that P. patens can be a sustainable and efficient production platform of artemisinin that without further modifications allow for industrial scale production. A stable supply of artemisinin will lower the price of artemisinin-based treatments, hence become more affordable to the lower income communities most affected by malaria; an important step towards containment of this deadly disease threatening millions every year.

Staphylococcus aureus in Some Brazilian Dairy Industries: Changes of Contamination and Diversity
Staphylococcus aureus, a major food-poisoning pathogen, is a common contaminant in dairy industries worldwide, including in Brazil. We determined the occurrence of S. aureus in five dairies in Brazil over 8 months. Of 421 samples, 31 (7.4%) were positive for S. aureus and prevalence varied from 0 to 63.3% between dairies. Sixty-six isolates from the 31 samples were typed by Multi-Locus Sequence Typing to determine if these isolates were persistent or continuously reintroduced. Seven known sequence types (STs), ST1, ST5, ST30, ST97, ST126, ST188 and ST398, and four new ST were identified, ST3531, ST3540, ST3562 and ST3534. Clonal complex (CC) 1 (including the four new ST), known as an epidemic clone, was the dominant CC. However, there were no indications of persistence of particular ST. The resistance toward 11 antibiotic compounds was assessed. Twelve profiles were generated with 75.8% of strains being sensitive to all antibiotic classes and no Methicillin-resistant S. aureus (MRSA) strains were found. The enterotoxin-encoding genes involved in food-poisoning, e.g., sea, sed, see, and seg were targeted by PCR. The two toxin-encoding genes, sed and see, were not detected. Only three strains (4.5%) harbored seg and two of these also harbored sea. Despite the isolates being Methicillin-sensitive S. aureus (MSSA), the presence of CC1 clones in the processing environment, including some harboring enterotoxin encoding genes, is of concern and hygiene must have high priority to reduce contamination.
Structure-based discovery of novel US28 small molecule ligands with different modes of action

The human cytomegalovirus-encoded G protein-coupled receptor US28 is a constitutively active receptor, which can recognize various chemokines. Despite the recent determination of its 2.9 Ångstrom crystal structure, potent and US28-specific tool compounds are still scarce. Here, we used structural information from a refined US28: VUF2274 complex for virtual screening of >12 million commercially available small molecule compounds. Using a combined receptor-and ligand-based approach, we tested 98 of the top 0.1% ranked compounds, revealing novel chemotypes as compared to the similar to 1.45 million known ligands in the ChEMBL database. Two compounds were confirmed as agonist and inverse agonist, respectively, in both IP accumulation and Ca2+ mobilization assays. The screening setup presented in this work is computationally inexpensive and therefore particularly useful in an academic setting as it enables-simultaneous testing in binding as well as in different functional assays and/or-species without actual chemical synthesis.
Supplementation of docosahexaenoic acid (DHA), vitamin D₃ and uridine in combination with six weeks of cognitive and motor training in prepubescent children: a pilot study

Background Learning and memory have been shown to be influenced by combination of dietary supplements and exercise in animal models, but there is little available evidence from human subjects. The aim of this pilot study was to investigate the effect of combining a motor- and cognitive exercise program with dietary supplementation consisting of 500 mg docosahexaenoic acid (DHA), 10 μg vitamin D₃ and 1000 mg uridine (DDU-supplement) in 16 prepubescent children (age 8–11 years). Methods We designed a randomized, placebo-controlled, double-blinded study lasting 6 weeks in which DDU-supplement or placebo was ingested daily. During the intervention period, all children trained approximately 30 min 3 days/week using an internet-based cognitive and motor training program (Miti). Prior to and post the intervention period dietary record, blood sampling, physical exercise tests and motor and cognitive tests were performed. Results Fourteen of the 16 children completed the intervention and ingested the supplement as required. 6 weeks DDU-supplementation resulted in a significant increase in the blood concentration of vitamin D₂+₃ and DHA (p=0.023 and p<0.001, respectively). Power calculation based on one of the cognitive tasks revealed a proper sample size of 26 children.

Conclusion All children showed improved performance in the trained motor- and cognitive tasks, but it was not possible to demonstrate any significant effects on the cognitive tests from the dietary supplementation. However, DDU-supplementation did result in increased blood concentration of DHA and vitamin D₂+₃. Trial registration Clinical
Surfing of bacterial droplets: *Bacillus subtilis* sliding revisited

Hennes et al. (1) report on the collective slipping of Bacillus subtilis colonies across the agar surface, termed "colony surfing." We read this article with great interest. However, we understand that specific points require a more detailed discussion. We would like to highlight complementary biological observations on this area previously published by us and others but omitted by Hennes et al. (1) with the aim of bringing about a common terminology that facilitates understanding between the biophysics and the microbiology communities.

Bacterial movement on surfaces can be powered by various active appendages, such as flagella, pili, or interaction of cytoskeletal and focal membrane complexes, …

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**General information**

**State:** Published

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**Pages:** E8802-E8802

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SWITCH: a dynamic CRISPR tool for genome engineering and metabolic pathway control for cell factory construction in Saccharomyces cerevisiae

Background

The yeast Saccharomyces cerevisiae is increasingly used as a cell factory. However, cell factory construction time is a major obstacle towards using yeast for bio-production. Hence, tools to speed up cell factory construction are desirable.
Results
In this study, we have developed a new Cas9/dCas9 based system, SWITCH, which allows Saccharomyces cerevisiae strains to iteratively alternate between a genetic engineering state and a pathway control state. Since Cas9 induced recombination events are crucial for SWITCH efficiency, we first developed a technique TAPE, which we have successfully used to address protospacer efficiency. As proof of concept of the use of SWITCH in cell factory construction, we have exploited the genetic engineering state of a SWITCH strain to insert the five genes necessary for naringenin production. Next, the naringenin cell factory was switched to the pathway control state where production was optimized by downregulating an essential gene TSC13, hence, reducing formation of a byproduct.

Conclusions
We have successfully integrated two CRISPR tools, one for genetic engineering and one for pathway control, into one system and successfully used it for cell factory construction.

General information
State: Published
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Synthesis of C-Glucosylated Octaketide Anthraquinones in Nicotiana benthamiana by Using a Multispecies-Based Biosynthetic Pathway

Carminic acid is a C-glucosylated octaketide anthraquinone and the main constituent of the natural dye carmine (E120), possessing unique coloring, stability, and solubility properties. Despite being used since ancient times, longstanding efforts to elucidate its route of biosynthesis have been unsuccessful. Herein, a novel combination of enzymes derived from a plant (Aloe arborescens, Aa), a bacterium (Streptomyces sp. R1128, St), and an insect (Dactylopius coccus, Dc) that allows for the biosynthesis of the C-glucosylated anthraquinone, dcll, a precursor for carminic acid, is reported. The pathway, which consists of AaOKS, StZhuI, StZhuJ, and DcUGT2, presents an alternative biosynthetic approach for the production of polyketides by using a type III polyketide synthase (PKS) and tailoring enzymes originating from a type II PKS system. The current study showcases the power of using transient expression in Nicotiana benthamiana for efficient and rapid identification of functional biosynthetic pathways, including both soluble and membrane-bound enzymes.

General information
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Society's strong dependence on fossil fuels and petroleum-based products leads not only to a rapid decline of natural oil reserves but contributes massively to global warming and environmental damage. This consequently urges society to look into more sustainable alternatives. Microorganisms present such sustainable alternative if converted into so-called microbial cell factories. Instead of crude oil, cell factories use renewable resources or waste products as source material. The challenge is, however, that microbial production needs to be economically feasible to compete with the classical chemical production. The development of a microbial cell factory typically takes up to 8 years of research and costs over $50 million. The production and selection of heterologous pathway proteins are major bottlenecks encountered in the construction of a cell factory. Thus, new approaches for the optimization of recombinant protein production and screening techniques with high capacity for the identification of the best performing enzymes are continually developed. This thesis aims to equip researchers with a fundamental knowledge about protein biosynthesis necessary for the
understanding of protein production bottlenecks. Moreover, the thesis guides through the possible causes of low protein yields and presents available approaches for optimization of the protein and the host. The main work presented in this thesis provides and applies a new synthetic biology approach for the optimization and selection of recombinant proteins. A major bottleneck during production is translation initiation. By creating sequence libraries of the translation initiation region, protein production can be improved substantially in Gram-negative and Gram-positive bacteria. The design of versatile and tuneable translational coupling devices and their fusion to antibiotic selection markers enables subsequent selection of high-expressing constructs. The approach is a simple and inexpensive alternative to advanced screening techniques. In addition, a second synthetic biology approach provides the means for fast and efficient plasmid backbone swapping and is a versatile tool for the design and construction of optimal protein production constructs.

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Authors: Rennig, M. (Intern), Nørholm, M. (Intern), Andersen, M. R. (Intern)
Number of pages: 194
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Projects:

Synthetic biology approaches for protein production optimization in bacterial cell factories
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**Targeted degradomics in protein terminomics and protease substrate discovery**

Targeted degradomics integrates positional information into mass spectrometry-based targeted proteomics workflows and thereby enables analysis of proteolytic cleavage events with unprecedented specificity and sensitivity. Rapid progress in establishment of protease-substrate relations provides extensive degradomics target lists that now can be tested with help of selected and parallel reaction monitoring (S/PRM) in complex biological systems, where proteases act in physiological environments. In this minireview, we describe the general principles of targeted degradomics, outline the generic experimental workflow of the methodology and highlight recent and future applications in protease research.

**General information**

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Taxonomic novelties in Aspergillus section Fumigati: A. tasmanicus sp. nov., induction of sexual state in A. turcosus and overview of related species

The phylogenetic position of two Aspergillus strains isolated from Australian soil and phenotypically resembling A. unilateralis was investigated by using multigene phylogeny based on β-tubulin (benA), calmodulin (CaM), actin (act), and RNA polymerase II second largest subunit (RPB2) genes. The analysis supported their placement into a separate lineage within a well-supported clade containing 10 other members of section Fumigati ("A. unilateralis clade"). Comparisons of extrolite profiles, taxonomically informative morphological and physiological characters were made, and it was discovered that the two strains can be differentiated from all relatives by their low maximum growth temperature, short stipes, and ornamentation of conidia. The data justified the proposal of a new species, A. tasmanicus sp. nov. Amplification of mating-type genes showed that the A. unilateralis clade contains five heterothallic species. Only the MAT1-1-1 idiomorph was detected among isolates of A. unilateralis, A. tasmanicus, and A. marvanovae, while isolates having both opposite mating types were detected in A. turcosus and A. nishimurae. The sexual state of A. turcosus was induced by mating experiments and is described in this study. Ascospores of this species were unique by their smooth to finely verrucose convex surface and two well-visible equatorial crests. Some exometabolites detected in A. marvanovae and A. tasmanicus are also indicative of a perfect state, thus supporting the hypothesis that these species have cryptic sexual cycles. The epitype and ex-epitype culture is designated for A. nishimurae to facilitate further taxonomic work with this species.

General information
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Organisations: Department of Biotechnology and Biomedicine, Fungal Chemodiversity, Charles University, Chiba University, EMSL Analytical, Inc., National Institute of Agricultural Science
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The aquaculture microbiome at the centre of business creation
Editorial: The microbiome as a source of new enterprises and job creation

General information
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Organisations: Department of Biotechnology and Biomedicine, Bacterial Ecophysiology and Biotechnology, Lallemand SAS
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The biodiversity of Aspergillus section Flavi and aflatoxins in the Brazilian peanut production chain
A total of 119 samples of peanut were collected throughout the peanut production chain in Sao Paulo State, Brazil. The peanut samples were directly plated for determination of percentages of infection and a polyphasic approach was used to identify Aspergillus section Flavi species. Further, the potential for aflatoxin production by the isolates was tested using the agar plug technique and the presence of aflatoxins in peanuts was assessed using an immunofluorimetry column followed by quantification using HPLC with reverse phase column and fluorescence detection. The limit of detection and quantification were 0.05 and 0.17 μg/kg for total aflatoxins, respectively. Four species of Aspergillus section Flavi were isolated: A. caelatus (11), A. flavus (515), A. parasiticus (17) and A. tamarii (13). All isolates of A. parasiticus were able to produce aflatoxin B and G whereas aflatoxin B was produced by 50% of A. flavus isolates. Aflatoxins were found in 12 samples at concentrations ranging from 0.3 to 100 μg/kg. The data reported in this study add information on the occurrence and biodiversity of fungi in peanuts at several stages of the production chain. The occurrence of aflatoxins is also of major relevance for continuous monitoring and assessment of likely exposure of consumers to aflatoxins through consumption of peanuts. (C) 2017 Elsevier Ltd. All rights reserved.

General information
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The cereal pathogen Fusarium pseudograminearum produces a mimic of cytokinin plant hormones

General information
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Organisations: Department of Biotechnology and Biomedicine, CSIRO, Aalborg University, Nagoya University, Karlsruhe Institute of Technology KIT, Aalborg Universitet København, University of Perugia
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Main Research Area: Technical/natural sciences

The gut microbiome in atherosclerotic cardiovascular disease
The gut microbiota has been linked to cardiovascular diseases. However, the composition and functional capacity of the gut microbiome in relation to cardiovascular diseases have not been systematically examined. Here, we perform a metagenome-wide association study on stools from 218 individuals with atherosclerotic cardiovascular disease (ACVD) and 187 healthy controls. The ACVD gut microbiome deviates from the healthy status by increased abundance of Enterobacteriaceae and Streptococcus spp. and, functionally, in the potential for metabolism or transport of several molecules important for cardiovascular health. Although drug treatment represents a confounding factor, ACVD status, and not current drug use, is the major distinguishing feature in this cohort. We identify common themes by comparison with gut microbiome data associated with other cardiometabolic diseases (obesity and type 2 diabetes), with liver cirrhosis, and rheumatoid arthritis. Our data represent a comprehensive resource for further investigations on the role of the gut microbiome in promoting or preventing ACVD as well as other related diseases. The gut microbiota may play a role in cardiovascular diseases. Here, the authors perform a metagenome-wide association study on stools from individuals with atherosclerotic cardiovascular disease and healthy controls, identifying microbial strains and functions associated with the disease.

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The identification and functional annotation of RNA structures conserved in vertebrates

Structured elements of RNA molecules are essential in, e.g., RNA stabilization, localization and protein interaction, and their conservation across species suggests a common functional role. We computationally screened vertebrate genomes for Conserved RNA Structures (CRSs), leveraging structure-based, rather than sequence-based, alignments. After careful correction for sequence identity and GC content, we predict ~516k human genomic regions containing CRSs. We find that a substantial fraction of human-mouse CRS regions (i) co-localize consistently with binding sites of the same RNA binding proteins (RBPs) or (ii) are transcribed in corresponding tissues. Additionally, a CaptureSeq experiment revealed expression of many of our CRS regions in human fetal brain, including 662 novel ones. For selected human and mouse candidate pairs, qRT-PCR and in vitro RNA structure probing supported both shared expression and shared structure despite low abundance and low sequence identity. About 30k CRS regions are located near coding or long non-coding RNA genes or within enhancers. Structured (CRS overlapping) enhancer RNAs and extended 3’ ends have significantly increased expression levels over their non-structured counterparts. Our findings of transcribed uncharacterized regulatory regions that contain CRSs support their RNA-mediated functionality.
The Influence of the Toxin/Antitoxin mazEF on Growth and Survival of Listeria monocytogenes under Stress

A major factor in the resilience of Listeria monocytogenes is the alternative sigma factor B (σB). Type II Toxin/Antitoxin (TA) systems are also known to have a role in the bacterial stress response upon activation via the ClpP or Lon proteases. Directly upstream of the σB operon in L. monocytogenes is the TA system mazEF, which can cleave mRNA at UACMU sites. In this study, we showed that the mazEF TA locus does not affect the level of persister formation during treatment with antibiotics in lethal doses, but exerts different effects according to the sub-inhibitory stress added. Growth of a ΔmazEF mutant was enhanced relative to the wildtype in the presence of sub-inhibitory norfloxacin and at 42 °C, but was decreased when challenged with ampicillin and gentamicin. In contrast to studies in Staphylococcus aureus, we found that the mazEF locus did not affect transcription of genes within the σB operon, but MazEF effected the expression of the σB-dependent genes opuCA and lmo0880, with a 0.22 and 0.05 fold change, respectively, compared to the wildtype under sub-inhibitory norfloxacin conditions. How exactly this system operates remains an open question, however, our data indicates it is not analogous to the system of S. aureus, suggesting a novel mode of action for MazEF in L. monocytogenes.
The maternal microbiome during pregnancy and allergic disease in the offspring

There is substantial epidemiological and mechanistic evidence that the increase in allergic disease and asthma in many parts of the world in part relates to changes in microbial exposures and diet acting via the composition and metabolic products of the intestinal microbiome. The majority of research in this field has focused on the gut microbiome during infancy, but it is increasingly clear that the maternal microbiome during pregnancy also has a key role in preventing an allergy-prone immune phenotype in the offspring. The mechanisms by which the maternal microbiome influences the developing fetal immune system include alignment between the maternal and infant regulatory immune status and transplacental passage of microbial metabolites and IgG. Interplay between microbial stimulatory factors such as lipopolysaccharides and regulatory factors such as short-chain fatty acids may also influence on fetal immune development. However, our understanding of these pathways is at an early stage and further mechanistic studies are needed. There are also no data from human studies relating the composition and metabolic activity of the maternal microbiome during pregnancy to the offspring's immune status at birth and risk of allergic disease. Improved knowledge of these pathways may inform novel strategies for tackling the increase in allergic disorders in the modern world.

General information
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The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases
Reports on bacteria detected in maternal fluids during pregnancy are typically associated with adverse consequences, and whether the female reproductive tract harbours distinct microbial communities beyond the vagina has been a matter of debate. Here we systematically sample the microbiota within the female reproductive tract in 110 women of reproductive age, and examine the nature of colonisation by 16S rRNA gene amplicon sequencing and cultivation. We find distinct microbial communities in cervical canal, uterus, fallopian tubes and peritoneal fluid, differing from that of the vagina. The results reflect a microbiota continuum along the female reproductive tract, indicative of a non-sterile environment. We also identify microbial taxa and potential functions that correlate with the menstrual cycle or are over-represented in subjects with adenomyosis or infertility due to endometriosis. The study provides insight into the nature of the vagino-uterine microbiome, and suggests that surveying the vaginal or cervical microbiota might be useful for detection of common diseases in the upper reproductive tract.

Whether the female reproductive tract harbours distinct microbiomes beyond the vagina has been a matter of debate. Here, the authors show a subject-specific continuity in microbial communities at six sites along the female reproductive tract, indicative of a non-sterile environment.

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Therapeutic Vaccine Against Primate Papillomavirus Infections of the Cervix

Currently available prophylactic vaccines have no therapeutic efficacy for preexisting human papillomavirus (HPVs) infections, do not target all oncogenic HPVs and are insufficient to eliminate the burden of HPV induced cancer. We aim to develop an alternative HPV vaccine which is broadly effective and capable of clearing preexisting infection. In an initial attempt to develop a broadly reactive therapeutic vaccine, we designed a putative papillomavirus (PV) ancestor antigen (circulating sequence derived antigenic sequences E1E2-CDSE1E2) based on the conserved E1 and E2 protein sequences from existing oncogenic HPV strains. This antigen was found to be as related to circulating oncogenic Macaca fascicularis papillomaviruses (MfPVs) as to oncogenic HPVs. The CDSE1E2 antigen was fused to a T-cell adjuvant and encoded in chimpanzee 3 and 63 adenoviral vectors. We first showed that the combination of these 2 vaccines induced long-lasting potent CDSE1E2 specific T cell responses in outbred mice. This prime-boost regimen was then tested in female macaques naturally infected with MfPVs. All immunized animals (16/16) responded to the vaccine antigen but with reduced cross-reactivity against existing PVs. Preexisting MfPV infections did not prime vaccine inducible immune responses. Importantly, immunized oncogenic MfPV type 3 (MfPV3) infected animals that responded toward MfPV3 were able to diminish cervical MfPV3 DNA content. Although insufficient breadth was achieved, our results suggest that a relevant level of E1E2 specific T cell immunity is achievable and might be sufficient for the elimination of PV infection. Importantly, naturally infected macaques, offer a relevant model for testing vaccines aimed at eliminating mucosal PV infections.
The Reducing Capacity of Thioredoxin on Oxidized Thiols in Boiled Wort

Free thiol-containing proteins are suggested to work as antioxidants in beer, but the majority of thiols in wort are present in their oxidized form as disulfides and are therefore not active as antioxidants. Thioredoxin, a disulfide-reducing protein, is released into the wort from some yeast strains during fermentation. The capacity of the thioredoxin enzyme system (thioredoxin, thioredoxin reductase, NADPH) to reduce oxidized thiols in boiled wort under fermentation-like conditions was studied. Free thiols were quantitated in boiled wort samples by derivatization with ThioGlo1 and fluorescence detection of thiol-derivatives. When boiled wort was incubated with all components of the thioredoxin system at pH 7.0 and 25 °C for 60 min under anaerobic conditions, the free thiol concentration increased from 25 to 224 μM. At pH values similar to wort (pH 5.7) and beer (pH 4.5), the thioredoxin system was also capable of increasing the free thiol concentration, although with lower efficiency to 187 and 170 μM, respectively. The presence of sulfite, an important antioxidant in beer secreted by the yeast during fermentation, was found to inactivate thioredoxin by sulfitolysis. Reduction of oxidized thiols by the thioredoxin system was therefore only found to be efficient in the absence of sulfite.

General information
State: Published
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Number of pages: 6
The resistome of important human pathogens

Genes capable of conferring resistance to clinically used antibiotics have been found in many different natural environments. However, a concise overview of the resistance genes found in common human bacterial pathogens is lacking, which complicates risk ranking of environmental reservoirs. Here, we present an analysis of potential antibiotic resistance genes in the 17 most common bacterial pathogens isolated from humans. We analyzed more than 20,000 bacterial genomes and defined a clinical resistome as the set of resistance genes found across these genomes. Using this database, we uncovered the co-occurrence frequencies of the resistance gene clusters within each species enabling identification of co-dissemination and co-selection patterns. The resistance genes identified in this study represent the subset of the environmental resistome that is clinically relevant and the dataset and approach provides a baseline for further investigations into the abundance of clinically relevant resistance genes across different environments. To facilitate an easy overview the data is presented at the species level at www.resistome.biosustain.dtu.dk.

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Organisations: Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Research Groups, Department of Biotechnology and Biomedicine
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The Role of Functional Amyloids in Multicellular Growth and Development of Gram-Positive Bacteria

Amyloid fibrils play pivotal roles in all domains of life. In bacteria, these fibrillar structures are often part of an extracellular matrix that surrounds the producing organism and thereby provides protection to harsh environmental conditions. Here, we discuss the role of amyloid fibrils in the two distant Gram-positive bacteria, Streptomyces coelicolor and Bacillus subtilis. We describe how amyloid fibrils contribute to a multitude of developmental processes in each of these systems, including multicellular growth and community development. Despite this variety of tasks, we know surprisingly little about how their assembly is organized to fulfill all these roles.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Friedrich-Schiller-Universität Jena, Leiden University
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Within the CAZy database, there are 81 carbohydrate-binding module (CBM) families. A CBM represents a non-catalytic domain in a modular arrangement of glycoside hydrolases (GHs). The present in silico study has been focused on starch-binding domains from the family CBM41 that are usually part of pullulanases from the α-amylase family GH13. Currently there are more than 1,600 sequences classified in the family CBM41, almost exclusively from Bacteria, and so a study was undertaken in an effort to divide the members into relevant groups (subfamilies) and also to contribute to the evolutionary picture of family CBM41. The CBM41 members adopt a β-sandwich fold (∼100 residues) with one carbohydrate-binding site formed by the side-chains of three aromatic residues that interact with carbohydrate. The family CBM41 can be divided into two basic subdivisions, distinguished from each other by a characteristic sequence pattern or motif of the three essential aromatics as follows: (i) "W-W−10aa-W" (the so-called Streptococcus/Klebsiella-type); and (ii) "W-W−30aa-W" (Thermotoga-type). Based on our bioinformatics analysis it is clear that the first and second positions of the motif can be occupied by aromatic residues (Phe, Tyr, His) other than tryptophan, resulting in the existence of six different carbohydrate-binding CBM41 groups, that reflect mostly differences in taxonomy, but which should retain the ability to bind an α-glucan. In addition, three more groups have been proposed that, although lacking the crucial aromatic motif, could possibly employ other residues from remaining parts of their sequence for binding carbohydrate. This article is protected by copyright. All rights reserved.
The structure of Lactococcus lactis thioredoxin reductase reveals molecular features of photo-oxidative damage

The NADPH-dependent homodimeric flavoenzyme thioredoxin reductase (TrxR) provides reducing equivalents to thioredoxin, a key regulator of various cellular redox processes. Crystal structures of photo-inactivated thioredoxin...
reductase (TrxR) from the Gram-positive bacterium Lactococcus lactis have been determined. These structures reveal novel molecular features that provide further insight into the mechanisms behind the sensitivity of this enzyme toward visible light. We propose that a pocket on the si-face of the isalloxazine ring accommodates oxygen that reacts with photo-excited FAD generating superoxide and a flavin radical that oxidize the isalloxazine ring C7α methyl group and a nearby tyrosine residue. This tyrosine and key residues surrounding the oxygen pocket are conserved in enzymes from related bacteria, including pathogens such as Staphylococcus aureus. Photo-sensitivity may thus be a widespread feature among bacterial TrxR with the described characteristics, which affords applications in clinical photo-therapy of drug-resistant bacteria.

Trajectories and Drivers of Genome Evolution in Surface-Associated Marine Phaeobacter

The extent of genome divergence and the evolutionary events leading to speciation of marine bacteria have mostly been studied for (locally) abundant, free-living groups. The genus Phaeobacter is found on different marine surfaces, seems to
occupy geographically disjunct habitats, and is involved in different biotic interactions, and was therefore targeted in the present study. The analysis of the chromosomes of 32 closely related but geographically spread Phaeobacter strains revealed an exceptionally large, highly syntenic core genome. The flexible gene pool is constantly but slightly expanding across all Phaeobacter lineages. The horizontally transferred genes mostly originated from bacteria of the Roseobacter group and horizontal transfer most likely was mediated by gene transfer agents. No evidence for geographic isolation and habitat specificity of the different phylogenomic Phaeobacter clades was detected based on the sources of isolation. In contrast, the functional gene repertoire and physiological traits of different phylogenomic Phaeobacter clades were sufficiently distinct to suggest an adaptation to an associated lifestyle with algae, to additional nutrient sources, or toxic heavy metals. Our study reveals that the evolutionary trajectories of surface-associated marine bacteria can differ significantly from free-living marine bacteria or marine generalists.
Transcriptional rewiring in human dendritic cells by the gut microbial metabolite butyrate is associated with propagation of a tissue-sustaining type 2-like immune response

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Relations
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Prediction of endotoxin variants in the human gut microbiome and their relation to metabolic disease
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Two distinct metacommunities characterize the gut microbiota in Crohn's disease patients
The inflammatory intestinal disorder Crohn's disease (CD) has become a health challenge worldwide. The gut microbiota closely interacts with the host immune system, but its functional impact in CD is unclear. Except for studies on a small number of CD patients, analyses of the gut microbiota in CD have used 16S rDNA amplicon sequencing. Here we employed metagenomic shotgun sequencing to provide a detailed characterization of the compositional and functional features of the CD microbiota, comprising also unannotated bacteria, and investigated its modulation by exclusive enteral nutrition (EEN). Based on signature taxa, CD microbiotas clustered into two distinct metacommunities indicating individual variability in CD microbiome structure. Metacommunity-specific functional shifts in CD showed enrichment in producers of the pro-inflammatory hexa-acylated lipopolysaccharide variant and a reduction in the potential to synthesize short chain fatty acids. Disruption of ecological networks was evident in CD, coupled with reduction in growth rates of many bacterial species. Short-term EEN elicited limited impact on the overall composition of the CD microbiota, although functional changes occurred following treatment. The microbiotas in CD patients can be stratified into two distinct metacommunities with the most severely perturbed metacommunity exhibiting functional potentials that deviate markedly from that of the healthy individuals with possible implication in relation to CD pathogenesis.

General information
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Ulcerative colitis, Crohn's disease, and irritable bowel syndrome have different profiles of extracellular matrix turnover, which also reflects disease activity in Crohn's disease

Increased protease activity is a key pathological feature of inflammatory bowel disease (IBD). However, the differences in extracellular matrix remodelling (ECM) in Crohn’s disease (CD) and ulcerative colitis (UC) are not well described. An increased understanding of the inflammatory processes may provide optimized disease monitoring and diagnostics. We investigated the tissue remodelling in IBD and IBS patients by using novel blood-based biomarkers reflecting ECM remodelling. Five ECM biomarkers (VICM, BGM, EL-NE, C5M, Pro-C5) were measured by competitive ELISAs in serum from 72 CD patients, 60 UC patients, 22 patients with irritable bowel syndrome (IBS), and 24 healthy donors. One-way analysis of variance, Mann-Whitney U-test, logistic regression models, and receiver operator characteristics (ROC) curve analysis was carried out to evaluate the diagnostic accuracy of the biomarkers. The ECM remodelling was significantly different in UC compared to CD. The best biomarker combination to differentiate UC from CD and colonic CD was BGM and VICM (AUC = 0.98, P5mg/mL), correlation of Pro-C5 (r = 0.36) with CDAI was slightly improved compared to CRP (r = 0.27) corrected for the use of immunosuppressant. Furthermore, BGM and EL-NE biomarkers were highly associated with colon inflammation in CD patients. ECM fragments of tissue remodelling in IBD affect UC and CD differently, and may aid in differentiating IBD from IBS (EL-NE, BGM, Pro-C5), and UC from CD patients (BGM, VICM). Formation of type V collagen is related to the level of inflammation in CD and may reflect disease activity in CD.

General information
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Understanding cardiac extracellular matrix remodeling to develop biomarkers of myocardial infarction outcomes

Cardiovascular Disease (CVD) is the most common cause of death in industrialized countries, and myocardial infarction (MI) is a major CVD with significant morbidity and mortality. Following MI, the left ventricle (LV) undergoes a wound healing response to ischemia that results in extracellular matrix (ECM) scar formation to replace necrotic myocytes. While ECM accumulation following MI is termed cardiac fibrosis, this is a generic term that does not differentiate between ECM accumulation that occurs in the infarct region to form a scar that is structurally necessary to preserve left ventricle (LV) wall integrity and ECM accumulation that increases LV wall stiffness to exacerbate dilation and stimulate the progression to heart failure. This review focuses on post-MI LV ECM remodeling, targeting the discussion on ECM biomarkers that could be useful for predicting MI outcomes.

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Unrestricted Mass Spectrometric Data Analysis for Identification, Localization, and Quantification of Oxidative Protein Modifications

Oxidation generates multiple diverse post-translational modifications resulting in changes in protein structure and function associated with a wide range of diseases. Of these modifications, carbonylations have often been used as hallmarks of oxidative damage. However, accumulating evidence supports the hypothesis that other oxidation products may be quantitatively more important under physiological conditions. To address this issue, we have developed a holistic mass spectrometry-based approach for the simultaneous identification, localization, and quantification of a broad range of oxidative modifications based on so-called "dependent peptides". The strategy involves unrestricted database searches with rigorous filtering focusing on oxidative modifications. The approach was applied to bovine serum albumin and human serum proteins subjected to metal ion-catalyzed oxidation, resulting in the identification of a wide range of different oxidative modifications. The most common modification in the oxidized samples is hydroxylation, but carbonylation, decarboxylation, and dihydroxylation are also abundant, while carbonylation showed the largest increase in abundance relative to nonoxidized samples. Site-specific localization of modified residues reveals several "oxidation hotspots" showing high levels of modification occupancy, including specific histidine, tryptophan, methionine, glutamate, and aspartate residues. The majority of the modifications, however, occur at low occupancy levels on a diversity of side chains.
Weight Change and Risk of Hyperglycemia in Elderly Women

Background

Hyperglycaemia increases the risk of type 2 diabetes, heart disease and stroke, and is influenced by weight. However, the impact of preceding weight change on blood glycemia levels in late-life is less well understood.

Aim

We studied the interplay between weight change and risk of hyperglycaemia in a prospective cohort of elderly women.

Methods

Elderly Caucasian women (age: 67.1 years at baseline, n=1173) enrolled in the Prospective Epidemiological Risk Factor study with baseline and 13-year follow-up measurements of BMI and fasting glucose levels (FPG) and no previous history of diabetes or impaired fasting glucose. Multivariate logistic regression was used to determine risk of hyperglycaemia (FPG ≥5.6 mmol/L or HbA1c ≥42 mmol/mol) in normalweight (BMI ≤25 kg/m2), overweight (BMI=25–29.9 kg/m2) and
overweight (BMI ≥ 30 kg/m²) women who either lost weight, were weight-stable or had gained weight at follow-up.

Results

Overweight and obese elderly women who had gained weight at follow-up presented an increased risk of hyperglycaemia, OR = 2.7 (1.6–4.6) and OR = 3.2 (1.5–6.8), compared to weight-stable normalweight women. Overweight and obese women who lost weight decreased their risk of hyperglycaemia to a level comparable to weight-stable normalweight women. Overweight and obese women with stable weight presented a two-fold increased risk of hyperglycaemia compared to normalweight weight-stable women.

Conclusions

Losing weight in late life had a positive effect on the risk of hyperglycaemia in overweight and obese women, while further, weight gain increased the risk of hyperglycaemia. The study highlights that strategies to reduce weight in obese and overweight elderly women could have a positive influence on disease burden in late-life.
What drives speciation? Examination into the evolutionary events of more than 100 Aspergillus species

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, Fungal Chemodiversity, Natural Product Discovery, Joint Genome Institute, Joint Bioenergy Institute
Authors: Rasmussen, J. L. N. (Intern), Vesth, T. C. (Intern), Theobald, S. (Intern), Kjaerbølling, I. (Intern), Frisvad, J. C. (Intern), Larsen, T. O. (Intern), Riley, R. (Ekstern), Salamov, A. (Ekstern), Grigoriev, I. V. (Ekstern), Baker, S. E. (Ekstern), Andersen, M. R. (Intern)
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Main Research Area: Technical/natural sciences
Electronic versions:
What_drives_speciation_Examination_into_the_evolutionary_events_of_more_than_100_Aspergillus_species.pdf
Publication: Research - peer-review › Conference abstract for conference – Annual report year: 2017

Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial

Objective To investigate whether a whole grain diet alters the gut microbiome and insulin sensitivity, as well as biomarkers of metabolic health and gut functionality. Design 60 Danish adults at risk of developing metabolic syndrome were included in a randomised cross-over trial with two 8-week dietary intervention periods comprising whole grain diet and refined grain diet, separated by a washout period of 6 weeks. The response to the interventions on the gut microbiome composition and insulin sensitivity as well as measures of glucose and lipid metabolism, gut functionality, inflammatory markers, anthropometry and urine metabolomics were assessed. Results 50 participants completed both periods with a whole grain intake of 179±50 g/day and 14±10 g/day in the whole grain and refined grain period, respectively. Compliance was confirmed by a difference in plasma alkylresorcinols (p<0.0001). Compared with refined grain, whole grain did not significantly alter glucose homeostasis and did not induce major changes in the faecal microbiome. Also, breath hydrogen levels, plasma short-chain fatty acids, intestinal integrity and intestinal transit time were not affected. The whole grain diet reduced body weight (p<0.0001), serum inflammatory markers, interleukin (IL)-6 (p=0.009) and C-reactive protein (p=0.003). The reduction in body weight was consistent with a reduction in energy intake, and IL-6 reduction was associated with the amount of whole grain consumed, in particular with intake of rye. Conclusion Compared with refined grain diet, whole grain diet did not alter insulin sensitivity and gut microbiome but reduced body weight and systemic low-grade inflammation.

General information
State: Accepted/In press
Organisations: National Food Institute, Research Group for Gut Microbiology and Immunology, Department of Bio and Health Informatics, Metagenomics, Disease Intelligence and Molecular Evolution, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Department of Chemical and Biochemical Engineering, Organic Chemistry, Center for BioProcess Engineering, DTU Multi Assay Core, Research Group for Analytical Food Chemistry, Copenhagen Center for Health Technology, University of Copenhagen, Chalmers University of Technology, Chalmers University of Technology, Bispebjerg University Hospital, Herlev and Gentofte Hospital, University of Auckland

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BFI (2017): BFI-level 2
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.29 SJR 7.074 SNIP 3.946
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 6.809 SNIP 3.968 CiteScore 9.1
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 6.104 SNIP 3.865 CiteScore 8.76
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.58 SNIP 3.459 CiteScore 7.6
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 4.066 SNIP 2.737 CiteScore 6.36
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.626 SNIP 2.612 CiteScore 5.74
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.527 SNIP 2.719
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.308 SNIP 2.729
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 3.275 SNIP 2.725
Scopus rating (2007): SJR 3.08 SNIP 2.703
Scopus rating (2006): SJR 3.056 SNIP 2.67
Scopus rating (2005): SJR 2.392 SNIP 2.402
Scopus rating (2004): SJR 2.25 SNIP 2.225
Scopus rating (2003): SJR 1.912 SNIP 2.197
Scopus rating (2002): SJR 1.994 SNIP 2.372
Scopus rating (2001): SJR 2.014 SNIP 2.32
Scopus rating (2000): SJR 1.396 SNIP 2.276
Scopus rating (1999): SJR 1.354 SNIP 2.122

Original language: English
colonic microflora, diet, immune response, inflammation, obesity

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DOIs:
X-ray diffraction analysis and in vitro characterization of the UAM2 protein from Oryza sativa

The role of seemingly non-enzymatic proteins in complexes interconverting UDP-arabinopyranose and UDP-arabinofuranose (UDP-arabinosemutases; UAMs) in the plant cytosol remains unknown. To shed light on their function, crystallographic and functional studies of the seemingly non-enzymatic UAM2 protein from Oryza sativa (OsUAM2) were undertaken. Here, X-ray diffraction data are reported, as well as analysis of the oligomeric state in the crystal and in solution. OsUAM2 crystallizes readily but forms highly radiation-sensitive crystals with limited diffraction power, requiring careful low-dose vector data acquisition. Using size-exclusion chromatography, it is shown that the protein is monomeric in solution. Finally, limited proteolysis was employed to demonstrate DTT-enhanced proteolytic digestion, indicating the existence of at least one intramolecular disulfide bridge or, alternatively, a requirement for a structural metal ion.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Joint Bioenergy Institute
Authors: Welner, D. H. (Intern), Tsai, A. Y. (Ekstern), DeGiovanni, A. M. (Ekstern), Scheller, H. V. (Ekstern), Adams, P. D. (Ekstern)
Pages: 241-245
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Main Research Area: Technical/natural sciences

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Journal: Acta Crystallographica. Section F: Structural Biology and Crystallization Communications
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Scopus rating (2017): SNIP 0.315 SJR 0.592
Web of Science (2017): Indexed yes
Scopus rating (2016): CiteScore 0.78 SJR 0.551 SNIP 0.309
Scopus rating (2015): SJR 0.505 SNIP 0.3 CiteScore 0.76
Scopus rating (2014): SJR 0.506 SNIP 0.297
Scopus rating (2013): SJR 0.548 SNIP 0.276
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Scopus rating (2012): SJR 0.565 SNIP 0.282
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Scopus rating (2011): SJR 0.505 SNIP 0.265
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
Scopus rating (2010): SJR 0.572 SNIP 0.283
Scopus rating (2009): SJR 0.488 SNIP 0.264
Scopus rating (2008): SJR 0.484 SNIP 0.215
Scopus rating (2007): SJR 0.583 SNIP 0.295
Scopus rating (2006): SJR 0.564 SNIP 0.293
Web of Science (2006): Indexed yes
Original language: English
Reversibly glycosylated polypeptide, Limited proteolysis, UDP-arabinopyranose mutase, Vector data collection
Electronic versions:
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DOIs:
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Publication: Research - peer-review › Journal article – Annual report year: 2017
Use of heterologous expressed polyketide synthase and small molecule foldases to make aromatic and cyclic compounds

A method for producing individual or libraries of tri- to pentadecaketide-derived aromatic compounds of interest by heterologous expression of polyketide synthase and aromatase/cyclase in a recombinant host cell.

General information
State: Published
Organisations: Department of Systems Biology, Biosynthetic Pathway Engineering, Eukaryotic Molecular Cell Biology
Publication date: 15 Dec 2016

Publication information
IPC: C12P 19/60 A1
Patent number: WO2016198623
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Main Research Area: Technical/natural sciences
Source: espacenet
Source-ID: WO2016198623
Publication: Research › Patent – Annual report year: 2016

Use of octaketide synthases to produce kermesic acid and flavokermesic acid

A method for producing an octaketide derived aromatic compound of interest (e.g. carminic acid), wherein the method comprises (I): heterologous expression of a recombinantly introduced Type III polyketide synthase (PKS) gene encoding an octaketide synthase (OKS) to obtain non-reduced octaketide in vivo within the recombinant host cell and (II): converting in vivo the non-reduced octaketide of step (I) into a C14-C34 aromatic compound of interest (e.g. carminic acid).

General information
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Organisations: Department of Biotechnology and Biomedicine, Eukaryotic Molecular Cell Biology, Biosynthetic Pathway Engineering
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Also published as: AU2016277469
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Source: espacenet
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Publication: Research › Patent – Annual report year: 2016

Glycosyltransferase glycosylating flavokermesic acid and/or kermesic acid

An isolated glycosyltransferase (GT) polypeptide capable of: (I) : conjugating glucose to flavokermesic acid (FK); and/or (II) : conjugating glucose to kermesic acid (KA) and use of this GT to e.g. make Carminic acid.
Background Rheumatoid arthritis (RA) and a subpopulation of osteoarthritis, inflammatory OA (IOA) are degenerative joint diseases with an inflammatory component. However, the degree of inflammation is much higher in RA than IOA. There are many signaling pathways involved with the inflammation-driven extracellular matrix (ECM) degradation in RA and IOA cartilage that have been suggested as anti-inflammatory targets. However, the results on joint structure in clinical trials have been varying. A better understanding of the intracellular signaling pathways and the downstream effect on ECM turnover could be beneficial for the selection of novel anti-inflammatory treatments for RA and IOA. Objectives The aim of this study was to investigate the direct effect of the anti-inflammatory inhibitors R406 (the active metabolite of Fostamatinib), Tofacitinib, TPCA-1 and SB203580 on the cartilage ECM turnover. Methods Full depth bovine cartilage ex vivo cultures were cultured for 3 weeks with OSM [10 ng/mL] and TNFα [2 ng/mL] (O+T) or together with R406, Tofacitinib or TPCA-1 at 10 μM and a two-fold dilution to 0.16 μM. SB203580 was tested at 3 μM, 1 μM and 0.3 μM. As negative control, untreated explants were included. The ECM turnover of the cartilage was assessed with the biomarkers; C2M, ProC2, AGNx1 and/or ARGS. Additionally, histology of the explants was examined with Safranin O and fast green staining. Results Aggrecanase mediated degradation of aggrecan was assessed with ARGS or AGNx1. The Syk inhibitor R406, the Jak inhibitor Tofacitinib, and the IKK inhibitor TPCA-1 inhibited the release of ARGS or AGNx1, while the p38 inhibitor, SB203580, had no effect. The turnover of type II collagen was measured by the formation of type II collagen (ProC2) and MMP-mediated degradation of type II collagen (C2M). The ratio between ProC2 and C2M was calculated for week 1–3. Tofacitinib and TPCA-1 increased the area under the curve (AUC) of ProC2/C2M significantly compared to O+T (p<0.001). SB203580 and R406 had no effect at 10 μM, 5 μM, 0.31 μM and 0.16 μM, but tended to increase ProC2/C2M at 2.5–0.625 μM compared to O+T (Figure 1). Safranin O and fast staining of the explants showed that O+T, SB203580 and 0.16 μM of R406, Tofacitinib, and TPCA-1 lead to loss of proteoglycans from the cartilage explants.
compared to the untreated explants. R406 at 10 μM retained the proteoglycans in the deep and middle zone of the cartilage, while the proteoglycans of the superficial layer was lost. 10 μM of Tofacitinib and TPCA-1 retained the proteoglycans in all layers of the cartilage explants. Conclusions The four inhibitors tested had a positive effect on the degradation of aggrecan and type II collagen. However, only Tofacitinib and TPCA-1 had an increased anabolic effect on type II collagen turnover. The anabolic effect from Tofacitinib and TPCA-1 on top of the anti-catabolic effect indicates that the chondrocytes can repair the cartilage during treatment opposite to the p38 inhibitor that inhibits the catabolic and the anabolic response.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Enzyme and Protein Chemistry, Nordic Bioscience A/S
Authors: Kjelgaard-Petersen, C. F. (Intern), Bay-Jensen, A. (Ekstern), Karsdal, M. (Ekstern), Hagglund, P. (Ekstern), Thudium, C. S. (Ekstern)
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Scopus rating (2016): CiteScore 8.02 SJR 7.083 SNIP 3.603
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 5.909 SNIP 3.255 CiteScore 7.4
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.505 SNIP 2.887 CiteScore 6.78
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 5.166 SNIP 2.889 CiteScore 7.28
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 5.031 SNIP 3.114 CiteScore 7.79
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 4.637 SNIP 2.741 CiteScore 7.16
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.859 SNIP 2.507
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.226 SNIP 2.196
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 2.248 SNIP 1.779
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.106 SNIP 1.787
Scopus rating (2006): SJR 1.947 SNIP 1.578
Scopus rating (2005): SJR 1.626 SNIP 1.869
Scopus rating (2004): SJR 1.426 SNIP 1.816
Scopus rating (2003): SJR 1.292 SNIP 1.625
Scopus rating (2002): SJR 1.279 SNIP 1.355
Aspergillus is monophyletic: Evidence from multiple gene phylogenies and extrolites profiles

Aspergillus is one of the economically most important fungal genera. Recently, the ICN adopted the single name nomenclature which has forced mycologists to choose one name for fungi (e.g. Aspergillus, Fusarium, Penicillium, etc.). Previously two proposals for the single name nomenclature in Aspergillus were presented: one attributes the name “Aspergillus” to clades comprising seven different teleomorphic names, by supporting the monophyly of this genus; the other proposes that Aspergillus is a non-monophyletic genus, by preserving the Aspergillus name only to species belonging to subgenus Circumdati and maintaining the sexual names in the other clades. The aim of our study was to test the monophyly of Aspergilli by two independent phylogenetic analyses using a multilocus phylogenetic approach. One test was run on the publicly available coding regions of six genes (RPB1, RPB2, Tsr1, Cct8, BenA, CaM), using 96 species of Penicillium, Aspergillus and related taxa. Bayesian (MrBayes) and Ultrafast Maximum Likelihood (IQ-Tree) and Rapid Maximum Likelihood (RaxML) analyses gave the same conclusion highly supporting the monophyly of Aspergillus. The other analyses were also performed by using publicly available data of the coding sequences of nine loci (18S rRNA, 5,8S rRNA, 28S rRNA (D1-D2), RPB1, RPB2, CaM, BenA, Tsr1, Cct8) of 204 different species. Both Bayesian (MrBayes) and Maximum Likelihood (RAxML) trees obtained by this second round of independent analyses strongly supported the monophyly of the genus Aspergillus. The stability test also confirmed the robustness of the results obtained. In conclusion, statistical analyses have rejected the hypothesis that the Aspergilli are non-monophyletic, and provided robust arguments that the genus is monophyletic and clearly separated from the monophyletic genus Penicillium. There is no phylogenetic evidence to split Aspergillus into several genera and the name Aspergillus can be used for all the species belonging to Aspergillus i.e. the clade comprising the subgenera Aspergillus, Circumdati, Fumigati, Nidulantes, section Cremei and certain species which were formerly part of the genera Phialosimplex and Polypaecilum. Section Cremei and the clade containing Polypaecilum and Phialosimplex are proposed as new subgenera of Aspergillus. The phylogenetic analysis also clearly shows that Aspergillus clavatoflavus and A. zonatus do not belong to the genus Aspergillus. Aspergillus clavatoflavus is therefore transferred to a new genus Aspergillago as Aspergillago clavatoflavus and A. zonatus was transferred to Penicilliosis as P. zonata. The subgenera of Aspergillus share similar extrolite profiles indicating that the genus is one large genus from a chemotaxonomical point of view. Morphological and ecophysiological characteristics of the species also strongly indicate that Aspergillus is a polythetic class in phenotypic characters.
Authors: Kocsubé, S. (Ekstern), Perrone, G. (Ekstern), Magistà, D. (Ekstern), Houbraken, J. (Ekstern), Varga, J. (Ekstern), Szigeti, G. (Ekstern), Hubka, V. (Ekstern), Hong, S. (Ekstern), Frisvad, J. C. (Intern), Samson, R. (Ekstern)

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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 14.62 SJR 7.735 SNIP 8.292
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): SJR 7.213 SNIP 8.482 CiteScore 15.65
BFI (2014): BFI-level 2
Scopus rating (2014): SJR 5.291 SNIP 6.503 CiteScore 11.76
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): SJR 3.786 SNIP 4.743 CiteScore 9.41
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.657 SNIP 3.951 CiteScore 7.86
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): SJR 3.882 SNIP 3.881 CiteScore 7.5
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.142 SNIP 3.224
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.925 SNIP 2.794
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.017 SNIP 2.528
Scopus rating (2007): SJR 2.328 SNIP 1.94
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.388 SNIP 1.596
Scopus rating (2005): SJR 0.783 SNIP 0.964
Scopus rating (2004): SJR 0.636 SNIP 1.512
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 0.809 SNIP 1.381
Scopus rating (2002): SJR 0.955 SNIP 2.891
Scopus rating (2001): SJR 1.384 SNIP 3.675
Scopus rating (2000): SJR 0.352 SNIP 2.104
Web of Science (2000): Indexed yes
Scopus rating (1999): SJR 2.788 SNIP 3.11

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Aspergillus, Multigene phylogeny, Monophyly, Nomenclature, Teleomorphs
Biotechnological Trends in Spider and Scorpion Antivenom Development

Spiders and scorpions are notorious for their fearful dispositions and their ability to inject venom into prey and predators, causing symptoms such as necrosis, paralysis, and excruciating pain. Information on venom composition and the toxins present in these species is growing due to an interest in using bioactive toxins from spiders and scorpions for drug discovery purposes and for solving crystal structures of membrane-embedded receptors. Additionally, the identification and isolation of a myriad of spider and scorpion toxins has allowed research within next generation antivenoms to progress at an increasingly faster pace. In this review, the current knowledge of spider and scorpion venoms is presented, followed by a discussion of all published biotechnological efforts within development of spider and scorpion antitoxins based on small molecules, antibodies and fragments thereof, and next generation immunization strategies. The increasing number of discovery and development efforts within this field may point towards an upcoming transition from serum-based antivenoms towards therapeutic solutions based on modern biotechnology.
Chemotaxonomy of the genus Stemphylium

General information
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Organisations: Department of Systems Biology, Natural Product Discovery, Fungal Degradation
Authors: Olsen, K. J. K. (Intern), Andersen, B. (Intern)
Number of pages: 1
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Main Research Area: Technical/natural sciences

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Scopus rating (2017): SNIP 0.964 SJR 0.581
Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.97 SJR 0.674 SNIP 0.945
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.638 SNIP 0.993 CiteScore 2.1
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.762 SNIP 1.13 CiteScore 2.15
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 0.798 SNIP 1.238 CiteScore 2.37
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 0.749 SNIP 1.117 CiteScore 2.35
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 0.707 SNIP 1.143 CiteScore 2.23
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.778 SNIP 1.137
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.777 SNIP 1.097
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.683 SNIP 0.971
Scopus rating (2007): SJR 0.839 SNIP 1.351
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.896 SNIP 1.322
Chondrocyte pro-proliferative compounds may utilize extracellular matrix remodeling processes to regenerate cartilage

General information
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Organisations: DTU Proteomics Core, Department of Biotechnology and Biomedicine, Nordic Bioscience A/S, Merck KGaA
Authors: Reker, D. (Ekstern), Kjelgaard-Petersen, C. F. (Intern), Gigout, A. (Ekstern), Ladel, C. (Ekstern), Siebuhr, A. (Ekstern), Michealis, M. (Ekstern), Karsdal, M. A. (Ekstern), Bay-Jensen, A. (Ekstern)
Number of pages: 1
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Conference: 2016 OARSI World Congress on Osteoarthritis Promoting Clinical and Basic Research in Osteoarthritis, Amsterdam, Netherlands, 31/03/2016 - 31/03/2016
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Web of Science (2017): Indexed Yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.62 SJR 2.267 SNIP 1.8
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.325 SNIP 1.698 CiteScore 4.57
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.29 SNIP 1.655 CiteScore 4.19
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.4 SNIP 1.779 CiteScore 4.74
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.006 SNIP 1.658 CiteScore 4.12
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.035 SNIP 1.564 CiteScore 3.99
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.852 SNIP 1.604
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.797 SNIP 1.534
CHO On A Detox: Removing By-Product Formation Through Cell Engineering

Chinese Hamster Ovary (CHO) cells are the preferred hosts for the production of therapeutic glycoproteins. However, there is a need for improvement of the bioprocesses towards increased cell growth and higher productivities without compromising the product quality. Efforts to obtain tailor-made products with the desired properties that meet the requirements of regulatory authorities are continuously being made. Of equal relevance is to develop methods to engineer cell lines with improved by-product metabolism.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories
Authors: Pereira, S. (Intern), Kildegaard, H. F. (Intern), Andersen, M. R. (Intern)
Number of pages: 1
Publication date: 2016
Event: Abstract from 1st ESACT Frontiers Retreat, Lyon, France.
Main Research Area: Technical/natural sciences
Electronic versions:
1st_ESACT_Frontiers_RetreatS.Pereira_Abstract.pdf

Curbing the development and spread of 'high risk' bacterial pathogens

MDR (multi-drug Resistant) og XDR (Extensively drug resistant) Pseudomonas aeruginosa clone types spread at alarming rates in hospital environments, and there is a clear need to limit the development and spread of these 'high risk' bacterial pathogens. I will describe our recent efforts to use genomic information to determine the mechanism by which these clone types evolve and spread, and our work on the development a web-based tool that can make identification of high risk clones faster in the clinical microbiology hospital departments. The rationale behind the development of this tool is that faster diagnosis will help to improve containment of the pathogen.

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Organisations: Department of Systems Biology, Infection Microbiology
Authors: Jelsbak, L. (Intern)
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http://www.sustain.dtu.dk/

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Sustain Abstract H-2
Current challenges of research on filamentous fungi in relation to human welfare and a sustainable bio-economy: a white paper

The EUROFUNG network is a virtual centre of multidisciplinary expertise in the field of fungal biotechnology. The first academic-industry Think Tank was hosted by EUROFUNG to summarise the state of the art and future challenges in fungal biology and biotechnology in the coming decade. Currently, fungal cell factories are important for bulk manufacturing of organic acids, proteins, enzymes, secondary metabolites and active pharmaceutical ingredients in white and red biotechnology. In contrast, fungal pathogens of humans kill more people than malaria or tuberculosis. Fungi are significantly impacting on global food security, damaging global crop production, causing disease in domesticated animals, and spoiling an estimated 10% of harvested crops. A number of challenges now need to be addressed to improve our strategies to control fungal pathogenicity and to optimise the use of fungi as sources for novel compounds and as cell factories for large scale manufacture of bio-based products. This white paper reports on the discussions of the Think Tank meeting and the suggestions made for moving fungal bio(techno)logy forward.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories, Department of Biotechnology, Eukaryotic Molecular Cell Biology, Technische Universität Berlin, Hans Knöll Institute, Georg-August-Universität Göttingen, University of Liverpool, Utrecht University, AB Enzymes GmbH, Novozymes A/S, Friedrich-Alexander-Universität Erlangen-Nürnberg, Centro de Investigaciones Biológicas, Leiden University, Ceratium Limited
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Defining carbohydrate binding of glucan phosphatases via Affinity gel electrophoresis
In plants, starch is the energy storage molecule that is readily broken down when needed. In animals, glycogen is the molecule that is used for energy storage. Both molecules are comprised of α-1, 4 linked glucose polymer chains and α-1,6 glucose branches that are tightly compacted. Our lab has determined the x-ray crystal structures of both plant and human glucan phosphatases and their enzymatic mechanisms. Despite this progress, we lacked the techniques to quickly and efficiently quantify their glucan phosphatase affinities for different substrates. The main objective of this study was to determine a technique to measure carbohydrate binding quickly and efficiently. We established a protocol to reproducibly and quantitatively measure the binding of the enzymes to glucans utilizing Affinity Gel Electrophoresis (AGE). The results show that the various glucan phosphatases possess differing abilities to bind to different glucan substrates. The plant glucan phosphatase SEX4 possesses a 50 fold higher affinity for the glucan amylopectin than LSF2, while SEX4 only possessed a 3 fold higher affinity for the glucan amyllose than LSF2. Mutations were made to the various domains of the plant and animal glucan phosphatases to determine which regions of the enzyme are most necessary for binding.
Detection of fungal growth and its influence on gypsum wallboard – in the process of creating sustainable building materials

General information
State: Published
Organisations: Department of Systems Biology, Fungal Degradation, Department of Civil Engineering, Section for Indoor Climate and Building Physics, Department of Mechanical Engineering, Materials and Surface Engineering, Eukaryotic Molecular Cell Biology, University of Sydney, Aarhus University, Aalborg University
Authors: Lewinska, A. M. (Intern), Lilje, O. (Ekstern), Foley, M. (Ekstern), Trimby, P. (Ekstern), Bjerring, M. (Ekstern), Vosegaard, T. (Forskerdatabase), Peuhkuri, R. H. (Forskerdatabase), Rode, C. (Intern), Grumsen, F. B. (Intern), Hoof, J. B. (Intern), Andersen, B. (Intern)
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Links: http://www.sustain.dtu.dk/

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Diversity and taxonomy of Chaetomium and chaetomium-like fungi from indoor environments
During a study of indoor fungi, 145 isolates belonging to Chaetomiaceae were cultured from air, swab and dust samples from 19 countries. Based on the phylogenetic analyses of DNA-directed RNA polymerase II second largest subunit (rpb2), β-tubulin (tub2), ITS and 28S large subunit (LSU) nrDNA sequences, together with morphological comparisons with related genera and species, 30 indoor taxa are recognised, of which 22 represent known species, seven are described as new, and one remains to be identified to species level. In our collection, 69 % of the indoor isolates with six species cluster with members of the Chaetomium globosum species complex, representing Chaetomium sensu stricto. The other indoor species fall into nine lineages that are separated from each other with several known chaetomiaceous genera occurring among them. No generic names are available for five of those lineages, and the following new genera are introduced here: Amesia with three indoor species, Arcopilus with one indoor species, Collariella with four indoor species, Dichotomopilus with seven indoor species and Ovatospora with two indoor species. The generic concept of Botryotrichum is expanded to include Emilimuelleria and the chaetomium-like species B. muromum (= Ch. muromum) in which two indoor species are included. The generic concept of Subramaniula is expanded to include several chaetomium-like taxa as well as one indoor species. Humicola is recognised as a distinct genus including two indoor taxa. According to this study, Ch. globosum is the most abundant Chaetomiaceae indoor species (74/145), followed by Ch. cochliodes (17/145), Ch. elatum (6/145) and B. piluliferum (5/145). The morphological diversity of indoor Chaetomiaceae as well as the morphological characteristics of the new genera are described and illustrated. This taxonomic study redefines the generic concept of Chaetomium and provides new insight into the phylogenetic relationships among different genera within Chaetomiaceae.

General information
State: Published
Organisations: Fungal Degradation, Department of Biotechnology and Biomedicine, DTU Metabolomics Core, CBS-KNAW Fungal Biodiversity Centre, Chinese Academy of Sciences
Authors: Wang, X. (Ekstern), Houbraken, J. (Ekstern), Groenewald, J. (Ekstern), Meijer, M. (Ekstern), Andersen, B. (Intern), Nielsen, K. (Intern), Crous, P. (Ekstern), Samson, R. (Ekstern)
Number of pages: 80
Pages: 145-224
Publication date: 2016
Effects of musculoskeletal related growth factors on cartilage extracellular matrix formation

General information
State: Published
Organisations: DTU Proteomics Core, Department of Biotechnology and Biomedicine, Nordic Bioscience A/S, Merck KGaA
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Number of pages: 1
Pages: S155
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Main Research Area: Technical/natural sciences

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Scopus rating (2016): CiteScore 4.62 SJR 2.267 SNIP 1.8
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 2.325 SNIP 1.698 CiteScore 4.57
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 2.29 SNIP 1.655 CiteScore 4.19
BFI (2013): BFI-level 1
Scopus rating (2013): SJR 2.4 SNIP 1.779 CiteScore 4.74
BFI (2012): BFI-level 1
Scopus rating (2012): SJR 2.006 SNIP 1.658 CiteScore 4.12
BFI (2011): BFI-level 1
Scopus rating (2011): SJR 2.035 SNIP 1.564 CiteScore 3.99
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.852 SNIP 1.604
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.797 SNIP 1.534
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.723 SNIP 1.452
Scopus rating (2007): SJR 1.768 SNIP 1.426
Scopus rating (2006): SJR 1.483 SNIP 1.515
Scopus rating (2005): SJR 1.827 SNIP 1.708
Scopus rating (2004): SJR 1.433 SNIP 1.445
Scopus rating (2003): SJR 1.272 SNIP 1.153
Scopus rating (2002): SJR 1.175 SNIP 1.022
Scopus rating (2001): SJR 0.998 SNIP 1.094
Scopus rating (2000): SJR 0.526 SNIP 1.183
Improving heterologous production of phenylpropanoids in \textit{Saccharomyces cerevisiae} by tackling an unwanted side reaction of Tsc13, an endogenous double-bond reductase

Phenylpropanoids, such as flavonoids and stilbenoids, are of great commercial interest, and their production in \textit{Saccharomyces cerevisiae} is a very promising strategy. However, to achieve commercially viable production, each step of the process must be optimised. We looked at carbon loss, known to occur in the heterologous flavonoid pathway in yeast, and identified an endogenous enzyme, the enoyl reductase Tsc13, which turned out to be responsible for the accumulation of phloretic acid via reduction of p-coumaroyl-CoA. Tsc13 is an essential enzyme involved in fatty acid synthesis and cannot be deleted. Hence, two approaches were adopted in an attempt to reduce the side activity without disrupting the natural function: site saturation mutagenesis identified a number of amino acid changes which slightly increased flavonoid production but without reducing the formation of the side product. Conversely, the complementation of TSC13 by a plant gene homologue essentially eliminated the unwanted side reaction, while retaining the productivity of phenylpropanoids in a simulated fed batch fermentation.
Increasing Oil Bodies in Physcomitrella patens by Overexpressing Oil Body-Associated Proteins

In bryophytes, reproductive organs contain large amount of oil bodies (OBs), the well-known lipidcontaining structures. OBs in spores are the most prominent and have been extensively studied. They are thought to be formed by budding off the outer layer of the endoplasmic reticulum membrane (ER) due to accumulation of neutral lipids between the leaflets of the phospholipid bilayer. In P. patens, the OBs are abundant in the mature sporophytes or during starvation, but are hardly observed in the vegetative stage. We overexpressed OB associated proteins such as oleosin, seipin, and fibrillin to increase the OB formation in P. patens vegetative tissue. As a result, we confirmed that the number of OBs were significantly increased in the protonemal cells compared to the wild type. These structures could be used to compartmentalize, synthetically made high-value compounds in green cells.

General information
State: Published
Organisations: Department of Systems Biology, Photosynthetic Cell Factories
Authors: Bae, H. (Intern), Peramuna, A. V. (Intern), Simonsen, H. T. (Intern)
Publication date: 2016
Main Research Area: Technical/natural sciences
Links: http://www.sustain.dtu.dk/
Influence of the medium and preferred cereal substrate on secondary metabolite production by species from Penicillium series Viridicata

General information
State: Published
Organisations: Fungal Chemodiversity, Department of Systems Biology, Metabolomics Platform, Fungal Chemodiversity
Authors: Hallas-Møller, M. (Intern), Nielsen, K. F. (Intern), Frisvad, J. C. (Intern)
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Scopus rating (2016): CiteScore 1.97 SJR 0.674 SNIP 0.945
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BFI (2014): BFI-level 1
Scopus rating (2014): SJR 0.762 SNIP 1.13 CiteScore 2.15
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Scopus rating (2012): SJR 0.749 SNIP 1.117 CiteScore 2.35
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ISI indexed (2011): ISI indexed yes
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Scopus rating (2010): SJR 0.778 SNIP 1.137
BFI (2009): BFI-level 1
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BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.683 SNIP 0.971
Scopus rating (2007): SJR 0.839 SNIP 1.351
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.896 SNIP 1.322
Scopus rating (2005): SJR 0.856 SNIP 1.154
Scopus rating (2004): SJR 0.788 SNIP 1.333
Scopus rating (2003): SJR 0.853 SNIP 1.334
Magnetosome production and functionalization

Magnetotactic bacteria produce magnetic particles, which enable them to migrate along the magnetic field lines in the environment they live in. The magnetic particles called magnetosomes are nanometer sized lipid bilayer encased uniform crystals of magnetite (Fe₃O₄) or greigite (Fe₃S₄). Their magnetic properties make them potentially useful in many biomedical and technological applications, such as drug delivery, magnetic resonance imaging, immunoassay and magnetic markers. Making them an alternative to chemically synthesized magnetic nanoparticles. Magnetospirillum gryphiswaldense MSR-1 as a model organism used to produce magnetosomes and is known to require a low dissolved oxygen (DO) concentration and iron during cultivation for magnetosome production. However, the relationship between these parameters and fermentation behavior is not well understood.

We will present a study where we investigate how the addition of iron impacts the physiology of the MSR-1 cells and the expression of key genes involved in the production of mangetosomes.

Furthermore, utilization of magnetosomes for applications as immunoassays requires the functionalization of the magnetosomes. Functionalization of the magnetosomes is achieved by attaching functional moieties to the magnetosome. We will present the work of functionalizing the magnetosomes for immunoassay by expressing IgG binding domains on the surface of magnetosomes.

General information
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Organisations: National Food Institute, Department of Systems Biology, Eukaryotic Molecular Cell Biology, Research Group for Microbial Biotechnology and Biorefining
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http://www.sustain.dtu.dk/

Bibliographical note
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Multi-omic profiling of EPO producing Chinese hamster ovary cell panel reveals metabolic adaptation to heterologous protein production

Heterologous protein production in CHO cells imposes a burden on the host cell metabolism and impact cellular physiology on a global scale. In this work, a multi-omics approach was applied to characterize the physiological impact of erythropoetin production, and discover production bottlenecks, in a panel of CHO-K1 cells in batch and chemostat culture.

General information
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Organisations: Novo Nordisk Foundation Center for Biosustainability, CHO Cell Line Engineering and Design, Quantitative Modeling of Cell Metabolism, Network Engineering of Eukaryotic Cell factories, Department of Bio and Health Informatics, Genomic Epidemiology, Department of Biotechnology and Biomedicine, Novo Nordisk A/S
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Plasma amino acid levels are elevated in young, healthy low birth weight men exposed to short-term high-fat overfeeding

Low birth weight (LBW) individuals exhibit a disproportionately increased, incomplete fatty acid oxidation and a decreased glucose oxidation, compared with normal birth weight (NBW) individuals, and furthermore have an increased risk of developing insulin resistance and type 2 diabetes. We hypothesized that changes in amino acid metabolism may occur parallel to alterations in fatty acid and glucose oxidation, and could contribute to insulin resistance. Therefore, we measured fasting plasma levels of 15 individual or pools of amino acids in 18 LBW and 25 NBW men after an isocaloric control diet and after a 5-day high-fat, high-calorie diet. We demonstrated that LBW and NBW men increased plasma alanine levels and decreased valine and leucine/isoleucine levels in response to overfeeding. Also, LBW men had higher alanine, proline, methionine, citrulline, and total amino acid levels after overfeeding compared with NBW men. Alanine and total amino acid levels tended to be negatively associated with the insulin-stimulated glucose uptake after overfeeding. Therefore, the higher amino acid levels in LBW men could be a consequence of their reduction in skeletal muscle insulin sensitivity due to overfeeding with a possible increased skeletal muscle proteolysis and/or could potentially contribute to an impaired insulin sensitivity. Furthermore, the alanine level was negatively associated with the plasma acetylcarnitine level and positively associated with the hepatic glucose production after overfeeding. Thus, the higher alanine level in LBW men could be accompanied by an increased anaplerotic formation of oxaloacetate and thereby an enhanced tricarboxylic acid cycle activity and as well an increased gluconeogenesis.

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Organisations: Department of Systems Biology, Systems Metabolic Lipidology, Copenhagen University Hospital, Duke University
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Scopus rating (2016): SJR 0.976 SNIP 0.663 CiteScore 0.69
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 0.826 SNIP 0.648
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Polyphasic taxonomy of Aspergillus section Cervini

Species belonging to Aspergillus section Cervini are characterised by radiate or short columnar, fawn coloured, uniseriate conidial heads. The morphology of the taxa in this section is very similar and isolates assigned to these species are frequently misidentified. In this study, a polyphasic approach was applied using morphological characters, extrolite data, temperature profiles and partial BenA, CaM and RPB2 sequences to examine the relationships within this section. Based on this taxonomic approach the section Cervini is resolved in ten species including six new species: A. acidohumus, A. christenseniae, A. novoguineensis, A. subnutans, A. transcarpathicus and A. wisconsinensis. A dichotomous key for the identification is provided.

General information

State: Published
Organisations: Fungal Chemodiversity, Department of Biotechnology and Biomedicine, CBS-KNAW Fungal Biodiversity Centre, Chinese Academy of Medical Sciences, University of Szeged, Novozymes China
Authors: Chen, A. (Ekstern), Varga, J. (Ekstern), Frisvad, J. C. (Intern), Jiang, X. (Ekstern), Samson, R. (Ekstern)
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BFI (2012): BFI-level 2
Scopus rating (2012): SJR 3.657 SNIP 3.951 CiteScore 7.86
ISI indexed (2012): ISI indexed yes
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BFI (2010): BFI-level 2
Scopus rating (2010): SJR 2.142 SNIP 3.224
Web of Science (2010): Indexed yes
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Scopus rating (2009): SJR 1.925 SNIP 2.794
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 2.017 SNIP 2.528
Scopus rating (2007): SJR 2.328 SNIP 1.94
Web of Science (2007): Indexed yes

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Prediction of secondary metabolite encoding genes based on chemical structure analysis

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Organisations: Department of Systems Biology, Natural Product Discovery, Department of Chemistry, Organic Chemistry, Eucaryotic Molecular Cell Biology, Metabolomics Platform, Ege University
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BFI (2016): BFI-level 1
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Web of Science (2014): Indexed yes
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Prospective Studies of Risk Factors Associated with Type 2 Diabetes, Cardiovascular Disease, and Mortality in Elderly Women

The world's population is ageing. With an increased life expectancy across the globe, more people will live into old age. Women outlive men averagely by four years, warranting an increased focus on healthy ageing in women. The demographic shift resulting in an increased fraction of elder individuals has given rise to concerns about whether the extra life years added are spent in good health or with disease conditions resulting in high impacts on health care systems, socioeconomic relations and on the individual level. The World Health Organization predicts the burden of non-communicable diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) to account for more than three-fourths of the total disease burden in middle and high-income countries before year 2030. Despite the identification of many risk factors for non-communicable diseases within the last decades, these risk factors remain the leading contributors to decreased healthy life expectancy in late-life, necessitating an increased focus on risk factors and non-communicable diseases specifically in elderly.

The studies constituting the foundation of this thesis aim to explore hypotheses focusing on known and novel risk factors and their relation to ageing, disease, and mortality in elderly Danish women. The studies are epidemiological in their character and based on data from the Prospective Epidemiological Risk Factor (PERF) study, a community-based cohort study on 5,855 elderly Danish women enrolled in year 2000 with a follow-up examination of 2,103 of the women in year 2013 (study I).

Data from the PERF cohort was used to evaluate whether the metabolic syndrome (MetS), a cluster definition of cardio-metabolic risk factors, is a valid and useful tool for prediction of future T2DM and CVD specifically in elderly women (study II). The study described how women fulfilling the current MetS criteria set by the International Diabetes Federation revealed an increased risk of future T2DM or CVD diagnosis. However, subjects who did not fulfil the definition criteria for MetS, but presented one or more of the MetS risk factors were likewise at increased risk. A further subdivision of the control group showed to increase the risk of T2DM to 6.3-fold (from 3.6-fold) and 1.7-fold for CVD (from 1.3-fold) for MetS-defined women when compared specifically to a control group solely including women with no MetS risk factors. Based on these risk estimates, it was concluded that employment of the MetS in elderly women should be focused only as a tool for identifying subjects with metabolic high-risk profiles. Further, the sum of risk factors was proposed to be equally
considered, as elderly women holding only a few MetS risk factors, were also at increased risk of T2DM and CVD.

The cohort was further used to explore how weight and weight change in late-life affected the risk of hyperglycaemia in elderly women (study III). The study presented a 2-fold increased risk of hyperglycaemia in overweight and obese elderly women compared to normalweight women after 13 years. In women who gained weight, the risk of hyperglycaemia in late-life was most profound for overweight and obese women resulting in a 2.7-fold increased risk of hyperglycaemia in overweight weight gainers and a 3.2-fold increased risk in obese weight gainers compared to normalweight weight-stable women. Contrarily, overweight and obese women who lost weight during the follow-up period decreased their risk of hyperglycaemia to a level comparable to women who stayed normalweight during the follow-up period.

The thesis rounds off by introducing a novel risk factor; matrix metalloproteinase (MMP)-mediated degradation of collagen type I (C1M) that was used in the description of mortality in elderly women (study IV). The study showed how increased MMP-mediated tissue degradation, as an independent risk factor, was associated with a 2-fold increase in all-cause mortality within three years of follow-up and a 1.5-fold increase in all-cause mortality up to nine years prior to death.

Overall, these studies contribute to the knowledge specifically demanded on women’s health in late-life by describing associations between known risk factors of the MetS and subsequent risk of T2DM and CVD. Further, by highlighting associations between hyperglycaemia, weight and weight change in late-life, and lastly by the evaluation of collagen type I degradation possibly being an important predisposition for increased mortality in elderly women.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Nordic Bioscience A/S, Odense University Hospital
Authors: Møller, K. D. (Intern), Pedersen, S. B. (Intern), Henriksen, K. (Ekstern), Karsdal, M. A. (Ekstern), Beck-Nielsen, H. (Ekstern)
Number of pages: 123
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Recycled organic building materials are prone to fungal growth

General information
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Authors: Andersen, B. (Intern)
Number of pages: 1
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Regulation of host metabolism and immunity by the gut microbiome
During recent years, central roles of the gut microbiome in metabolic and immunological diseases have been uncovered, and multiple studies have shown that bacterial-derived components shape host physiology and immune responses via direct cellular interactions. The intestinal immune system is crucial for the induction of effective immune responses against invading pathogens while simultaneously being vital for maintenance of homeostatic conditions. This balancing act requires a tightly regulated system that might be influenced by bacterial metabolites such as butyrate, since reduced frequencies of butyrate-producing species associate with various lifestyle-associated disorders.

In the present work, we used systems biology approaches to understand how bacterial components may associate with
metabolic disease and mediate phenotypic shifts in pro-inflammatory immune cells. First, we developed a computational framework for identifying bacteria that produce specific endotoxin variants with opposing immunological effects in metagenomic fecal samples. This framework was used to identify the endotoxin variant distribution amongst bacteria in the gut microbiome of Danes and Chinese with obesity and type 2 diabetes. We show for the first time that species producing pro-inflammatory endotoxin variants are vastly underrepresented in the gut microbiome compared to species producing non-inflammatory endotoxin and we identify country-specific gram-negative bacterial modules associated with insulin resistance. Second, we show that when the short-chain fatty acid butyrate is present under proinflammatory conditions, it induces a phenotypic switch in monocyte-derived dendritic cells to promote homeostasis through a potent inhibition of a type 1 immune response and induction of tissue-sustaining transcriptional programs. Collectively, these studies give insight into how intestinal microbes can affect their human host in a context-specific manner.

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Systems Metabolic Lipidology, Regulatory Genomics
Authors: Laursen, J. M. (Intern), Pedersen, S. B. (Intern), Hellgren, L. (Intern), Workman, C. (Intern)
Number of pages: 128
Publication date: 2016

Publication information
Publisher: Technical University of Denmark (DTU)
Original language: English
Main Research Area: Technical/natural sciences

Relations
Projects:
Regulation of host metabolism and immunity by the gut microbiome
Source: PublicationPreSubmission
Source-ID: 141053418
Publication: Research › Ph.D. thesis – Annual report year: 2018

Remodeling of the Tumor Microenvironment Predicts Increased Risk of Cancer in Postmenopausal Women: The Prospective Epidemiologic Risk Factor (PERF I) Study
Background: An altered tumor microenvironment is one of the earliest signs of cancer and an important driver of the disease. We have seen previously that biomarkers reflecting tumor microenvironment modifications, such as matrix metalloproteinase (MMP)-degraded type 1 collagen (C1M), MMP-degraded type IV collagen (C4M), and citrullinated and MMP-degraded vimentin (VICM), were higher in the serum of cancer patients than in healthy controls. However, it is not known if these biomarkers could predict an increased risk of cancer. The aim of this study was to investigate whether C1M, C4M, and VICM were elevated prior to diagnosis of solid cancers in a large prospective study.

Methods: Between 1999 and 2001, 5,855 postmenopausal Danish women ages 48 to 89 years enrolled in the Prospective Epidemiologic Risk Factor study. Baseline demographics and serum were collected at the time of registration. Follow up cancer diagnoses were obtained from the Danish Cancer Registry in 2014. Serum C1M, C4M, and VICM levels were measured by competitive ELISAs.

Results: A total of 881 women were diagnosed with solid cancers after baseline. C1M, C4M, and VICM levels were significantly elevated in women diagnosed less than 1 year after baseline. C1M and VICM, but not C4M, were independent predictors of increased risk of cancer.

Conclusion: C1M, C4M, and VICM are elevated prior to cancer diagnosis. C1M and VICM are both independent predictors of increased cancer risk.

Impact: C1M and VICM are predictors for increased risk of cancer. Cancer Epidemiol Biomarkers Prev; 25(9); 1348–55. ©2016 AACR.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Nordbic Bioscience A/S, University Hospital Herlev
Authors: Bager, C. L. (Intern), Willumsen, N. (Ekstern), Kehlet, S. N. (Intern), Hansen, H. B. (Ekstern), Bay-Jensen, A. (Ekstern), Leeming, D. J. (Ekstern), Møller, K. D. (Intern), Neergaard, J. (Intern), Christiansen, C. (Ekstern), Hegdall, E. (Ekstern), Karsdal, M. A. (Ekstern)
Pages: 1348-1355
Publication date: 2016
Main Research Area: Technical/natural sciences
Seamless gene editing in Aspergillus species, using CRISPR-Cas9

Many fungi are both excellent degraders of biomass and natural producers of industrially interesting compounds, making them good candidates for cell factories. Several members of the genus Aspergillus are successfully used as industrial cell factories for production of organic acids, enzymes and other primary or secondary metabolites, and many other Aspergilli are currently being sequenced and might possess traits making them similar suitable as potential cell factories. Yields from such cell factories can be greatly enhanced by employing genetic engineering strategies, however there are several obstacles slowing down the process.

The harnessing of the prokaryotic and archaeal immune mechanism CRISPR (clustered regularly interspaced short palindromic repeats) as a tool for genetic engineering in eukaryotes, has proved to be a powerful technology. CRISPR/Cas9 introduces specific DNA double strand breaks (DSB) with high precision, which in turn can be employed to efficiently stimulate gene targeting. Consisting of two components, an RNA guided nuclease Cas9 and a chimeric guide RNA (gRNA), a specific DSB can be produced in the host organism, which can be utilized to facilitate precise gene editing. The cleavage target site is determined by 20 base pairs (bp) in the gRNA, and by exchanging those 20 bp, Cas9 can be programmed to target a specific chromosomal location with few constraints. The technology has had a huge impact on genetic engineering of organisms, such as plants or mammalian cells where gene targeting is notoriously inefficient, but has only recently been adapted to filamentous fungi.

When using conventional strategies for genetic engineering in filamentous fungi, most strategies results in a genetic selection marker being left behind at the site of the edit, which can affect metabolism and negatively impact downstream processing. Here we present methods allowing for seamlessly inserting or deleting genes, for precisely introducing point mutations without changing the surrounding sequence, and a simple assay to easily identify efficient gRNAs. Together these methods provide a valuable addition to the genetic toolbox of several species of industrial relevant Aspergillus species, which can greatly accelerate the development of new fungal cell factories.

Serological biomarkers reflecting collagen remodeling of the tumor microenvironment are elevated in metastatic colorectal cancer

Targeting the DCIR Receptor with a TLR7 Agonist Specifically Activates Monocytes and DCs
Analysis showed that the effect of cell physiology was much more pronounced in the absence of the generally proposed stationary phase culture compared to an exponentially growing culture. Moreover, the type of culture used for the analysis affected the phenotypic variation, as heterogeneity was more pronounced when the population profile for this reporter strain was shown to be dependent on the type of medium. Chemically defined medium used for propagation of L. lactis resulted in a population profile which was problematic to analyze in relation to cell-to-cell growth rate variability. To investigate population heterogeneity in different types of microorganisms a Saccharomyces cerevisiae GFP reporter strain was analyzed. In this strain, a ribosomal protein promoter regulated the GFP expression. It was investigate on a single cell level, whether the used of inducible promoter showed that the degree of heterogeneity was slightly higher at intermediate inducer concentrations. Additionally, the effect of thermal stress on phenotypic heterogeneity was addressed by inflicting a heat stress to the B. subtilis GFP reporter strain. The increase in incubation temperature transient increased intermediate inducer concentrations. Additionally, the effect of thermal stress on phenotypic heterogeneity was addressed by inflicting a heat stress to the B. subtilis GFP reporter strain. The increase in incubation temperature transient increased intermediate inducer concentrations. Additionally, the effect of thermal stress on phenotypic heterogeneity was addressed by inflicting a heat stress to the B. subtilis GFP reporter strain. The increase in incubation temperature transient increased intermediate inducer concentrations. Additionally, the effect of thermal stress on phenotypic heterogeneity was addressed by inflicting a heat stress to the B. subtilis GFP reporter strain. The increase in incubation temperature transient increased intermediate inducer concentrations. 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addition of sodium chloride to the medium. In summary population heterogeneity in isogenic populations of microorganisms was investigated using different approaches. The primary approach used in this work was single cell analysis by flow cytometry. In the cell-to-cell growth rate variability analysis process it became obvious that procedures for quantification of heterogeneity was lacking. One of the main outcomes of this project was thus the development of procedures for non-statisticians on how to use flow cytometry data to quantify heterogeneity. We are confident that the results presented in this work, will assist the scientific community in quantifying heterogeneity. Finally, the findings in this study signify the importance of a proper experimental setup in order to achieve reproducible and hence valid data.

General information
State: Published
Organisations: Department of Systems Biology, Metabolic Signaling and Regulation, Metabolic Signaling and Regulation
Authors: Pedersen, A. E. (Intern), Martinussen, J. (Intern)
Number of pages: 187
Publication date: 2015

Publication information
Publisher: Department of Systems Biology, Technical University of Denmark
Original language: English
Main Research Area: Technical/natural sciences
Electronic versions:
Heterogeneity_in_isogenic.pdf

Relations
Projects:
Heterogeneity in isogenic populations of microorganisms
Publication: Research › Ph.D. thesis – Annual report year: 2016

Identification of Disease Relevant Post Translational Modifications of Proteins in Pulmonary Fibrosis as Novel Biochemical Marker Targets
Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease and is associated with a heterogeneous occurrence of fibrosis but the cause of the disease is still unknown. There is no cure and the two most promising drug candidates (pirenidone and nintedanib) only provide limited halt in disease progression and outcome. Biopsies are the standard tool in IPF diagnosis but they are time-consuming, highly invasive and often fail to provide a prognosis. Biopsies are also taken too late to provide an early diagnose that can alter outcome. Chest radiography and computed tomography are less invasive but also inadequate in specific diagnose. Thus new lung specific biomarkers are needed for the diagnosis and prognosis of IPF. Novel biomarkers would be best applicable if non-invasive and able to provide information not already accessible by other noninvasive tools such as spirometry, chest radiography and computed tomography. The levels of the two proteinases neutrophil elastase (NE) and matrix metalloproteinase-7 (MMP-7) are elevated in IPF in several studies. We believe that the activity of these proteases may be related to the progression of IPF. In the present work we aimed to discuss and highlight the roles of posttranslational modifications (PTMs) in the progression of IPF with special focus on proteolytic cleavage of lung proteins such as elastin. We also aimed to develop novel non-invasive elastin biomarkers that may contribute with higher sensitivity towards diagnosis of IPF. First, we developed biomarkers for NE-specific degradation of elastin. Monoclonal antibodies (mABs) were raised against immunogenic sites in the human elastin sequence. The mABs were screened for technical performance, specificity towards NE-degraded elastin and clinical relevance. The EL-NE mAB was selected as the best candidate for the quantification of NE-specific degradation of elastin and ELISA assay development was conducted resulting in the EL-NE assay. The assay was specific towards NE-degraded elastin and the EL-NE neo-epitope with limited reactivity towards intact elastin. Secondly, we developed biomarkers for matrix MMP-7 degradation of elastin. The screening and assay development was conducted using similar methodology to EL-NE. The ELM7 mAB was selected as the best candidate for the quantification of MMP-7-specific degradation of elastin. The assay was specific towards MMP-7-degraded elastin and the ELM7 neo-epitope with limited reactivity towards intact elastin. Finally, we tested the assays for clinical relevance in serum from patients diagnosed with IPF or lung cancer and healthy matched controls. Serum EL-NE- and ELM7 fragment levels were significantly elevated in IPF- and lung cancer patients compared to matched controls. In conclusion, we have developed two technically stable assays, EL-NE and ELM7, for the quantification of elastin degraded by NE and MMP-7 respectively. Both assays were protease specific. Initial clinical testing suggested clinical relevance of the assays in the quantification of the excessive lung extracellular remodelling occurring in pulmonary disorders, especially IPF.

General information
State: Published
Organisations: Enzyme and Protein Chemistry, Department of Systems Biology, Center for Biological Sequence Analysis, Proteomics Platform, Enzyme and Protein Chemistry, Nordic Bioscience A/S
Authors: Kristensen, J. H. (Intern), Hägglund, P. (Intern), Svensson, B. (Intern), Oersnes-Leeming, D. J. (Ekstern)
Number of pages: 128
Detection and identification of indoor fungi in water-damaged buildings is crucial for preventing and controlling fungal growth. This study focuses on a molecular method called DNA barcoding, which evaluates commonly used sequences in DNA barcoding for fungal species identification of Chaetomium and Stachybotrys. The existing DNA barcodes: ITS, SSU, LSU, B-TUB, CMD, RP and TEF-1α do not give satisfying species resolution to be considered as DNA barcodes for the two genera. Therefore, novel barcodes for them are needed. Barcode potentials, such as HOG1 and NAHA, were identified using bioinformatics and are being evaluated in the laboratory.

### General information
- **State:** Published
- **Organisations:** Department of Biotechnology and Biomedicine, Fungal Degradation, Eukaryotic Molecular Cell Biology, Department of Civil Engineering
- **Authors:** Lewinska, A. M. (Intern), Hoof, J. B. (Intern), Peuhkuri, R. H. (Intern), Rode, C. (Intern), Andersen, B. (Intern)
- **Number of pages:** 6
- **Pages:** 281-288
- **Publication date:** 2014
Antibiotic Subsistence by Pathogenic Bacteria

Concluding Remarks

References

General information
State: Published
Organisations: Department of Biotechnology and Biomedicine, Novo Nordisk Foundation Center for Biosustainability, Bacterial Synthetic Biology, Washington University in St. Louis
Authors: Dantas, G. (Ekstern), Sommer, M. O. A. (Intern)
Pages: 29-41
Publication date: 2011

Host publication information
Title of host publication: Antimicrobial Resistance in the Environment
Publisher: Wiley
ISBN (Print): 9780470905425
Chapter: 4
Main Research Area: Technical/natural sciences
DOI: 10.1002/9781118156247.ch4
Source: PublicationPreSubmission
Source-ID: 136921685
Publication: Research - peer-review › Book chapter – Annual report year: 2011

Projects:

Bioluminescence pathway in algae
This project investigates the synthesis of luciferin in bioluminescent dinoflagellates.

Photosynthetic Cell Factories
Department of Biotechnology and Biomedicine
Period: 02/01/2018 → 25/05/2018
Number of participants: 2
Project participant:
Ejlsted, Kristian (Intern)
Main Supervisor:
Simonsen, Henrik Toft (Intern)

Predictive and Accelerated Metabolic Engineering Network
PACMEN is a European training network, which offers excellent training in biotech research and innovation for 16 talented young scientists. PhD students will carry out cutting-edge research in metabolic engineering, modeling, systems and synthetic biology. In collaboration with industrial partners, they will create novel solutions for sustainable production of fuels and chemicals. The graduates will be prepared through research, business, and entrepreneurship training to launch their careers in industry or academia.

Novo Nordisk Foundation Center for Biosustainability

Yeast Cell Factories

Research Groups

Yeast Metabolic Engineering

Synthetic Biology Tools for Yeast

Eukaryotic Molecular Cell Biology
Period: 01/10/2016 → 30/09/2020
Number of participants: 12
Biotechnology
Acronym: PACMEN
Project Manager, organisational:
Lohmann, Ricarda (Intern)
Financing sources
Source: EU research programme (public)
Name of research programme: MSCA-ITN - Marie Skłodowska-Curie actions – International Training Networks
Web address: http://www.pacmen-itn.eu

Relations
Publications:
1. Lighting up yeast cell factories by transcription factor-based biosensors
2. Engineering microbial fatty acid metabolism for biofuels and biochemicals

Activities:

Best of both: A novel hybrid PRM/DIA method on the Q Exactive HF-X
Period: 2018
Simonas Savickas (Invited speaker)
Department of Biotechnology and Biomedicine
Degree of recognition: International

Related event
Nordic Proteomics Meeting
18/04/2018 → 20/04/2018
Activity: Talks and presentations › Conference presentations

Best of both: A novel hybrid PRM/DIA method on the Q Exactive HF-X
Period: 2018
Simonas Savickas (Speaker)
Department of Biotechnology and Biomedicine

Related external organisation
Thermo Fisher Scientific
United States
Activity: Talks and presentations › Talks and presentations in private or public companies and organisations

High-Throughput targeted degradomics analysis of matrix metalloproteinases network in murine skin using pressure cycling technology
Period: 2018
Simonas Savickas (Speaker)
Department of Biotechnology and Biomedicine
**35TH WINTER SCHOOL ON PROTEINASES AND INHIBITORS**
28/02/2018 → 04/03/2018
Activity: Talks and presentations › Conference presentations

**High-Throughput targeted degradomics analysis of matrix metalloproteinases network in murine skin using pressure cycling technology**
Period: 2018
Simonas Savickas (Speaker)
Department of Biotechnology and Biomedicine

**Related organisation**
High-Throughput targeted degradomics analysis of matrix metalloproteinases network in murine skin using pressure cycling technology
Savickas, S. (Speaker)
2018
Activity: Talks and presentations › Talks and presentations in private or public companies and organisations

**antismash hackathon**
Period: 27 Mar 2018 → 28 Mar 2018
Tilmann Weber (Organizer)
Kai Blin (Organizer)
Simon Shaw (Organizer)
Sebastian Theobald (Participant)
Omkar Satyavan Mohite (Participant)
Novo Nordisk Foundation Center for Biosustainability
New Bioactive Compounds
Network Engineering of Eukaryotic Cell factories

**Description**
Organization of an antiSMASH hackathon for developing the next versions of antiSMASH and the antiSMASH database
Degree of recognition: International

**Related event**
antismash hackathon
27/03/2018 → 28/03/2018
Kgs. Lyngby, Denmark
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

**Collapse of genetic division of labor and evolution of autonomy in pellicle biofilms**
Period: 21 Nov 2017
Ákos T. Kovács (Invited speaker)
Department of Biotechnology and Biomedicine

**Description**
Danish Biofilm Working Group meeting
Degree of recognition: Regional

**Related event**
Biofilm Working Group
21/11/2017 → 21/11/2017
Kgs. Lyngby, Denmark
Activity: Talks and presentations › Conference presentations
Danish Microbiological Society
Period: 13 Nov 2017
Eva Sonnenschein (Participant)
Department of Biotechnology and Biomedicine
Bacterial Ecophysiology and Biotechnology

**Description**
DMS Congress 2017
Degree of recognition: National

**Related event**
Danish Microbiological Society: DMS Congress 2017
13/11/2017 → 13/11/2017
Copenhagen, Denmark
Activity: Attending an event › Participating in or organising a conference

**Stress induced biofilms of Bacillus subtilis: the role of ppGpp**
Period: 13 Nov 2017
Ákos T. Kovács (Invited speaker)
Department of Biotechnology and Biomedicine
Degree of recognition: National

**Related event**
The Annual Congress of The Danish Microbiological Society (DMS)
13/11/2017 → 13/11/2017
Copenhagen, Denmark
Activity: Talks and presentations › Conference presentations

**Engineering CHO Cells For Improved Medium Catabolism – A Network Approach**
Period: 7 Nov 2017
Mikael Rørdam Andersen (Invited speaker)
Department of Biotechnology and Biomedicine
Network Engineering of Eukaryotic Cell factories
Degree of recognition: International

**Related event**
Annual Cell Culture & Bioprocessing Congress
07/11/2017 → …
Activity: Talks and presentations › Conference presentations

**Interconnected activities and functions of matrix metalloproteinases at the wound edge**
Period: 29 Oct 2017
Simonas Savickas (Other)
Department of Biotechnology and Biomedicine

**Related event**
International Proteolysis Society Meeting
27/10/2017 → 02/11/2017
Banff, Canada
Activity: Talks and presentations › Conference presentations

**Applications of Network Biology to Fungal Biotechnology**
Period: 18 Oct 2017
Mikael Rørdam Andersen (Invited speaker)
Department of Biotechnology and Biomedicine
Network Engineering of Eukaryotic Cell factories
Degree of recognition: International

Related event

Central European Forum for Microbiology
18/10/2017 → 20/10/2017
Activity: Talks and presentations › Conference presentations

Abundance of Cell-cell Communication Networks Governs Adaptation to Distinct Life-styles
Period: 16 Oct 2017 → 19 Oct 2017
Ákos T. Kovács (Speaker)
Department of Biotechnology and Biomedicine
Degree of recognition: International

Related event

6th ASM Conference on Cell-Cell Communication in Bacteria (CCCB)
16/10/2017 → 19/10/2017
Athens, GA, United States
Activity: Talks and presentations › Conference presentations

European Commission (External organisation)
Period: 5 Oct 2017 → 23 Dec 2017
Susanne Brix Pedersen (Chairman)
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International

Related external organisation

European Commission
Belgium
Activity: Membership › Membership of commitees, commissions, boards, councils, associations, organisations, or similar

Collapse of genetic division of labor and evolution of autonomy in pellicle biofilms
Period: 19 Sep 2017 → 22 Sep 2017
Ákos T. Kovács (Invited speaker)
Department of Biotechnology and Biomedicine

Related event

EuroBiofilms 2017
19/09/2017 → 22/09/2017
Amsterdam, Netherlands
Activity: Talks and presentations › Conference presentations

Interconnected activities and functions of matrix metalloproteinases at the wound edge.
Period: 16 Sep 2017
Simonas Savickas (Other)
Department of Biotechnology and Biomedicine
Degree of recognition: International

Related event

16th Human Proteome Organisation World Congress
Description
Crude oil reserves are becoming increasingly scarce, and biorefinery systems that integrate biomass conversion processes and equipment to produce fuels, power, and chemicals from annually renewable resources are a promising technology to move away from a petroleum-based society to a biomass-based society. One interesting biomass that has not been extensively utilized is marine biomass such as brown macroalgae (kelp). The composition of brown macroalgae includes up to 55% dry weight of the carbohydrates laminarin, mannitol and alginate, and it does not contain lignin. Hence, macroalgae are a very promising feedstock for microbial conversion of all carbohydrates into biofuels and valuable chemicals. Despite the presence of this native catabolic pathway, many yeast strains cannot catabolize mannitol or require adaptation to do so.

In this study a screening of thirty six strains, isolated from different sources, was performed. The strains were grown on complex and minimal media with mannitol as a main carbon source. Fifteen strains showed growth on complex media-mannitol (CM-mannitol) and just three diploid strains were capable to growth on minimal media-mannitol (MM-mannitol). After a couple of months of Adaptive Laboratory Evolution (ALE) three Saccharomyces cerevisiae diploid strains (YPS606, RM11 and T7) were successfully adapted to grow on MM-mannitol. Despite the efforts, the laboratory CENPK113-7D strain was unable to utilize this sugar alcohol as a carbon source.

Degree of recognition: International

Documents:
Poster_jplo

Related event
28th International Conference on Yeast Genetics and Molecular Biology
27/08/2017 → 01/09/2017
Prague, Czech Republic
Activity: Talks and presentations › Conference presentations
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International

Related event

European Society of Cardiology
26/08/2017 → 30/08/2017
Barcelona, Spain
Activity: Attending an event › Participating in or organising a conference

ESEB 2017
Period: 22 Aug 2017
Ákos T. Kovács (Chairman)
Department of Biotechnology and Biomedicine

Description
Symposium 15: Experimental evolution in complex environments
Degree of recognition: International

Related event

ESEB 2017: Congress of the European Society of Evolutionary Biology
20/08/2017 → 25/08/2017
Groningen, Netherlands
Activity: Attending an event › Participating in or organising workshops, courses, seminars etc.

Gordons Research Seminar
Period: 16 Jul 2017 → 23 Aug 2017
Signe Holm Nielsen (Organizer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology

Related event

Gordons Research Seminar: Collagens
16/07/2017 → 22/07/2017
New London, United States
Activity: Attending an event › Participating in or organising a conference

European Renal Association – European Dialysis and Transplantation Association
Period: 3 Jun 2017 → 6 Jun 2017
Signe Holm Nielsen (Organizer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology

Related event

European Renal Association – European Dialysis and Transplantation Association: 54th congress
03/06/2017 → 06/06/2017
Madrid, Spain
Activity: Attending an event › Participating in or organising a conference

Tar-Eating Bacterial Duo may Transform Toxic Compounds into New Usable Materials
Period: 16 May 2017
Sünje Johanna Pamp (Participant)
Department of Biotechnology and Biomedicine
Danish researchers have sequenced and analyzed the genome of a bacterium that can feed off coal tar. It lives in symbiosis with another bacterium that can recycle its partner’s waste. Researchers hope that this sustainable bacterial duo can transform toxic substances into useful materials. Nevertheless, mapping the genome also led to an unpleasant surprise.

Mapping drivers of phenotypic adaptation in clinical isolates of *Pseudomonas aeruginosa*

Period: 10 May 2017
Jennifer Bartell (Speaker)
Department of Biotechnology and Biomedicine
Novo Nordisk Foundation Center for Biosustainability
Infection Microbiology

**Related event**

**Copenhagen Bioscience Conference 2017: Data-Driven Biotechnology - Bench, Bioreactor and Bedside**
07/05/2017 → 10/05/2017
Hillerød, Denmark
Activity: Talks and presentations › Conference presentations

**Transcriptional rewiring in human dendritic cells by the gut microbial metabolite butyrate is associated with propagation of a tissue-sustaining type 2-like immune response**

Period: 4 May 2017
Janne Marie Moll (Lecturer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International

**Related event**

**In-FLAME 6th Annual Workshop**
03/05/2017 → 05/05/2017
New York, United States
Activity: Talks and presentations › Conference presentations

**Prediction of endotoxin variants in the human gut microbiome and their relation to metabolic disease**

Period: 3 May 2017
Janne Marie Moll (Lecturer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology

**Related event**

**In-FLAME 6th Annual Workshop**
03/05/2017 → 05/05/2017
Microbial Networks: Using a systems approach to interpret microbe function, adaptation, and interaction
Period: 26 Apr 2017
Jennifer Bartell (Speaker)
Department of Biotechnology and Biomedicine
Novo Nordisk Foundation Center for Biosustainability
Infection Microbiology

Related event
Whitaker Enrichment Seminar 2017
24/04/2017 → 28/04/2017
Lisbon, Portugal
Activity: Talks and presentations › Conference presentations

Interconnected activities and functions of matrix metalloproteinases at the wound edge.
Period: 21 Apr 2017
Simonas Savickas (Speaker)
Department of Biotechnology and Biomedicine
Degree of recognition: National

Related event
LS2 Swiss Proteomics Meeting
01/10/2016 → …
Activity: Talks and presentations › Conference presentations

Whole-genus Association Analysis – Using Hundreds of Microbial Genomes for Linking of Phenotype to Genotypes
Period: 22 Mar 2017
Mikael Rørdam Andersen (Invited speaker)
Department of Biotechnology and Biomedicine
Network Engineering of Eukaryotic Cell factories
Degree of recognition: International

Related event
Genomics of Energy & Environment Meeting
21/03/2017 → 24/03/2017
United States
Activity: Talks and presentations › Conference presentations

Expansions and reductions in fungal primary metabolism across 100 fungal species
Period: 15 Mar 2017
Mikael Rørdam Andersen (Invited speaker)
Department of Biotechnology and Biomedicine
Network Engineering of Eukaryotic Cell factories
Degree of recognition: International

Related event
29th Fungal Genetics Conference
14/03/2017 → 19/03/2017
Pacific Grove, United States
Activity: Talks and presentations › Conference presentations
29th Fungal Genetics Conference
Period: 14 Mar 2017 → 19 Mar 2017
Jane Lind Nybo Rasmussen (Speaker)
Department of Biotechnology and Biomedicine
Network Engineering of Eukaryotic Cell factories
Degree of recognition: International
Documents: 29FGC_Abstract_Book
Links: http://www.genetics-gsa.org/fungal/2017/

Related event
29th Fungal Genetics Conference
14/03/2017 → 19/03/2017
Pacific Grove, United States
Activity: Talks and presentations › Conference presentations

Systems modeling of adapting Pseudomonas aeruginosa during chronic infections
Period: 10 Mar 2017
Jennifer Bartell (Speaker)
Department of Biotechnology and Biomedicine
Novo Nordisk Foundation Center for Biosustainability
Infection Microbiology

Related event
Dansk Selskab for Klinisk Microbiologi
10/03/2017 → 11/03/2017
Nyborg, Denmark
Activity: Talks and presentations › Conference presentations

Interconnected activities and functions of matrix metalloproteinases at the wound edge.
Period: 27 Feb 2017
Simonas Savickas (Speaker)
Department of Biotechnology and Biomedicine

Related event
35TH WINTER SCHOOL ON PROTEINASES AND INHIBITORS
22/02/2017 → 26/02/2017
Tiers, Italy
Activity: Talks and presentations › Conference presentations

Deakin University
Period: 13 Feb 2017 → 3 Mar 2017
Susanne Brix Pedersen (Visiting researcher)
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International
Activity: Visiting an external institution › Visiting another research institution

American Society of Nephrology: Kidney Week
Period: 3 Nov 2016 → 6 Nov 2016
Signe Holm Nielsen (Organizer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology

Related event

American Society of Nephrology: Kidney Week
03/11/2016 → 06/11/2016
Chicago, United States
Activity: Attending an event › Participating in or organising a conference

American Society of Matrix Biology
Signe Holm Nielsen (Organizer)
Department of Biotechnology and Biomedicine
Disease Systems Immunology

Related event

American Society of Matrix Biology: Biennial Meeting
28/10/2016 → 07/12/2016
Activity: Attending an event › Participating in or organising a conference

The Function of Tumor Microenvironment in Cancer Progression, San Diego 2016
Period: 7 Jan 2016 → 10 Jan 2016
Stephanie Nina Kehlet (Speaker)
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International
Documents:
SNK_CRC abstract_final

Related event

The Function of Tumor Microenvironment in Cancer Progression, San Diego 2016
07/01/2016 → 10/01/2016
Activity: Talks and presentations › Conference presentations

European Cancer Conference (ECC)
Period: 25 Sep 2015 → 29 Sep 2015
Stephanie Nina Kehlet (Speaker)
Department of Biotechnology and Biomedicine
Disease Systems Immunology
Degree of recognition: International
Documents:
PERF - C1M associates with Tumor burden V3 28APR2015SNK

Related event

European Cancer Conference (ECC)
25/09/2015 → 29/09/2015
Activity: Talks and presentations › Conference presentations

Prizes:
DTU Teacher of the year 2017
Birgitte Andersen (Recipient)
Department of Biotechnology and Biomedicine, Fungal Degradation

Details
Awarded date: 28 Apr 2017
Prize: Prizes, scholarships, distinctions

International Proteolysis society travel award
Simonas Savickas (Recipient)
Department of Biotechnology and Biomedicine

Details
Awarded date: 2017
Degree of recognition: International
Prize: Prizes, scholarships, distinctions

Life Science Switzerland travel award
Simonas Savickas (Recipient)
Department of Biotechnology and Biomedicine

Details
Awarded date: 2017
Degree of recognition: International
Prize: Prizes, scholarships, distinctions

Poster prize
Jane Lind Nybo Rasmussen (Recipient)
Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories

Details
Awarded date: 19 Mar 2017
Degree of recognition: International
Granting Organisations: Genetics Society of America
event: 29th Fungal Genetics Conference
Prize: Prizes, scholarships, distinctions

Poster prize
Jane Lind Nybo Rasmussen (Recipient)
Department of Biotechnology and Biomedicine, Network Engineering of Eukaryotic Cell factories

Details
Awarded date: 6 Apr 2016
Degree of recognition: International
event: 13th European Conference on Fungal Genetics
Prize: Prizes, scholarships, distinctions

Press clippings:

Lighting in public places can in future be replaced with bioluminescent algae
Kristian Ejlsted & Henrik Toft Simonsen
04/04/2018
Department of Biotechnology and Biomedicine, Photosynthetic Cell Factories

Media contribution (1)

Lighting in public places can in future be replaced with bioluminescent algae
04/04/2018
Videnskab.dk (National), Denmark, Web
Kristian Ejlsted
https://videnskab.dk/naturvidenskab/fremtidens-gadelamper-kan-vaere-oplyst-af-alger
A new study from DTU suggests that knowledge about the bioluminescent system of dinoflagellates can help us create sustainable natural lighting in cities in the future.
Scientists solve 30-year old mystery on how resistance genes spread
15/06/2017

Description
Press release on our Nature Communication paper on the dissemination of antibiotic resistance genes; Press release / article covered by multiple news outlets, blogs and individual tweeters (https://www.nature.com/articles/ncomms15784/metrics)
Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, Research Groups, Bacterial Synthetic Biology, Department of Biotechnology and Biomedicine

Media contribution (1)

Scientists solve 30-year old mystery on how resistance genes spread
15/06/2017
DTU Biosustainability Homepage (International), Denmark, Web
Anne Wärme Lykke
http://www.biosustain.dtu.dk/english/nyhedsbase/2017/06/antibiotic-genes?id=9b924680-693f-47e2-8d7f-03c6cecfe473
Novo Nordisk Foundation Center for Biosustainability, New Bioactive Compounds, Department of Biotechnology and Biomedicine, Bacterial Synthetic Biology, Research Groups

Relations
Research outputs:
Dissemination of antibiotic resistance genes from antibiotic producers to pathogens
Projects:
Integration of Informatics and Metabolic Engineering for the discovery of Novel Antibiotics
Press / Media