A biomarker of collagen type I degradation is associated with cardiovascular events and mortality in patients with atherosclerosis

Objective Atherosclerosis is characterized by accumulation of lipids, cells and extracellular matrix (ECM) proteins in the arterial wall. Collagen type I (COL1), a component of the arterial ECM, is cleaved by matrix metalloproteinases (MMPs) and known to be remodelled in atherosclerosis. We explored whether the MMP-mediated COL1 biomarker, C1M, was associated with cardiovascular events, cardiovascular mortality and all-cause mortality in a large prospective cohort of patients with known atherosclerosis. Methods Serum from 787 patients who underwent a carotid endarterectomy was included. Circulating levels of C1M were measured in serum. A total of 473 patients were followed for 6 years after surgery. Associations between C1M and incidence of cardiovascular events, cardiovascular mortality and all-cause mortality were assessed by Kaplan-Meier curves and Cox regression analysis. Results A total of 101 (21.4%) patients suffered from nonfatal cardiovascular events during the follow-up period, and 64 (13.5%) patients died. Of these, 39 (60.9%) died from cardiovascular diseases. Patients with C1M levels above the median were significantly associated with cardiovascular events, cardiovascular mortality and all-cause mortality (P < 0.001, P = 0.004 and P < 0.001, respectively). C1M was included in the final model for prediction of cardiovascular events (HR 2.15, 95% CI 1.40-3.32, P = 0.001), cardiovascular mortality (HR 2.20, 95% CI 1.07-4.51, P = 0.031) and all-cause mortality (HR 2.98 95% CI 1.67-5.33, P < 0.001). Conclusions In patients with atherosclerotic carotid lesions, high levels of C1M predicted cardiovascular events, cardiovascular mortality and all-cause mortality. These findings emphasize the importance of remodelling mechanisms in atherosclerosis that are now becoming more and more explored.
Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children

The gut microbiota evolves from birth and is influenced by events such as birth mode, type of infant feeding, and maternal and infant antibiotics use. However, we still have a gap in our understanding of gut microbiota development in older children, and to what extent early events and pre-school lifestyle modulate the composition of the gut microbiota, and how this impinges on whole body metabolic regulation in school-age children. Taking advantage of the KOALA Birth Cohort Study, a long-term prospective birth cohort in the Netherlands with extensive collection of high-quality host metadata, we applied shotgun metagenomics sequencing and systematically investigated the gut microbiota of children at 6-9 years of age. We demonstrated an overall adult-like gut microbiota in the 281 Dutch school-age children and identified 3 enterotypes dominated by the genera Bacteroides, Prevotella, and Bifidobacterium, respectively. Importantly, we found that breastfeeding duration in early life and pre-school dietary lifestyle correlated with the composition and functional competences of the gut microbiota in the children at school age. The correlations between pre-school dietary lifestyle and metabolic phenotypes exhibited a striking enterotype dependency. Thus, an inverse correlation between high dietary fiber consumption and low plasma insulin levels was only observed in individuals with the Bacteroides and Prevotella enterotypes, but not in Bifidobacterium enterotype individuals in whom the gut microbiota displayed overall lower microbial gene richness, alpha-diversity, functional potential for complex carbohydrate fermentation, and butyrate and succinate production. High total fat consumption and elevated plasma free fatty acid levels in the Bifidobacterium enterotype are associated with the co-occurrence of Streptococcus. Our work highlights the persistent effects of breastfeeding duration and pre-school dietary lifestyle in affecting the gut microbiota in school-age children and reveals distinct compositional and functional potential in children according to enterotypes. The findings underscore enterotype-specific links between the host metabolic phenotypes and dietary patterns, emphasizing the importance of microbiome-based stratification when investigating metabolic responses to diets. Future diet intervention studies are clearly warranted to examine gut microbiota-host relationships to promote knowledge-based recommendations in relation to improving metabolic health in children.
Interplay between food and gut microbiota in health and disease
Numerous microorganisms colonize the human gastrointestinal tract playing pivotal roles in relation to digestion and absorption of dietary components. They biotransform food components and produce metabolites, which in combination with food components shape and modulate the host immune system and metabolic responses. Reciprocally, the diet modulates the composition and functional capacity of the gut microbiota, which subsequently influence host biochemical processes establishing a system of mutual interaction and inter-dependency. Macronutrients, fibers, as well as polyphenols and prebiotics are strong drivers shaping the composition of the gut microbiota. Especially, short-chain fatty acids produced from ingested fibers and tryptophan metabolites are key in modulating host immune responses. Since reciprocal interactions between diet, host, and microbiota are personal, understanding this complex network of interactions calls for novel use of large datasets and the implementation of machine learning algorithms and artificial intelligence. In this review, we aim to provide a base for future investigations of how interactions between food components and gut microbiota may influence or even determine human health and disease.

Levels of Systemic Low-grade Inflammation in Pregnant Mothers and Their Offspring are Correlated
High sensitivity C-reactive protein (hs-CRP) is a marker of systemic low-grade inflammation and associated with chronic inflammatory diseases. It is unknown whether maternal and infant hs-CRP levels are correlated and little is known about risk factors in early childhood. Hs-CRP were measured in mothers during pregnancy week 24 (N = 690), and one-week postpartum (N = 675) and in their children age 6 mo (N = 640) enrolled in the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC 2010) cohort. The risk factor analysis included anthropometrics, environmental exposures and CRP-Genetic Risk Score (GRS). Mother’s body mass index (BMI), use of antibiotics, smoking, cesarean delivery and season were associated with higher maternal hs-CRP level, whereas higher social circumstances were associated with lower hs-CRP level (p < 0.05). Child’s BMI, siblings, bacterial airway colonization, current infection, CRP-genetic risk score and season were associated with higher hs-CRP at age 6 mo (all p < 0.05). Mother’s hs-CRP level in pregnancy week 24 was associated with hs-CRP level in the child at 6 mo: β-coefficient = 0.11 [95% CI: 0.01–0.20], R² = 0.22, p = 0.03. The association was unchanged adjusted for all significant risk factors. Systemic low-grade inflammation in pregnant mothers and their offspring is correlated independently of BMI, environmental exposures and genetic risk factors.
Naïve regulatory T cells in infancy: Associations with perinatal factors and development of food allergy

In previous studies, deficits in regulatory T-cell (Treg) number and function at birth have been linked with subsequent allergic disease. However, longitudinal studies, that account for relevant perinatal factors, are required. The aim of this study was to investigate the relationship between perinatal factors, naïve Treg (nTreg) over the first postnatal year, and development of food allergy. In a birth cohort (n=1074), the proportion of nTreg in the CD4+ T-cell compartment was measured by flow cytometry at birth (n=463), six (n=600) and twelve (n=675) months. IgE-mediated food allergy was determined by food challenge at one year. Associations between perinatal factors (gestation, labour, sex, birth size), nTreg at each time point and food allergy at 1 year were examined by linear regression. A higher proportion of nTreg at birth, larger birth size and male sex were each associated with higher nTreg in infancy. Exposure to labour, as compared to delivery by pre-labour Caesarean section, was associated with a transient decrease nTreg. Infants that developed food allergy had decreased nTreg at birth, and the labour-associated decrease in nTreg at birth was more evident among infants with subsequent food allergy. Mode of birth was not associated with risk of food allergy and there was no evidence that nTreg at either six or twelve months were related to food allergy. The proportion of nTreg at birth is a major determinant of the proportion present throughout infancy, highlighting the importance of prenatal immune development. Exposure to the inflammatory stimulus of labour appears to reveal differences in immune function among infants at risk of food allergy. This article is protected by copyright. All rights reserved.

Serological Assessment of Activated Fibroblasts by alpha-Smooth Muscle Actin (α-SMA): A Noninvasive Biomarker of Activated Fibroblasts in Lung Disorders

OBJECTIVES: Remodeling of the extracellular matrix (ECM) is a key event in different lung disorders, such as fibrosis and cancer. The most common cell type in the connective tissue is fibroblasts, which transdifferentiate into myofibroblasts upon activation. All myofibroblasts express α-SMA, which has been found to be upregulated in lung fibrosis and cancer. We evaluated the potential of α-SMA as a noninvasive biomarker of activated fibroblasts in lung fibrosis and cancer.

METHODS: A monoclonal antibody was raised against the N-terminal of α-SMA, and a novel competitive enzyme-linked immunosorbent assay (ELISA) measuring α-SMA was developed and technically characterized. Levels of α-SMA were
measured in the fibroblast model, “scar-in-a-jar” and in serum from patients with idiopathic pulmonary fibrosis (IPF), chronic obstructive lung disorder (COPD) and non–small cell lung cancer (NSCLC) belonging to two different cohorts.

**RESULTS:** The novel α-SMA assay was developed and validated as technically robust. Based on the scar-in-a-jar results, α-SMA was only present in the fibroblasts activated by TGF-β. In cohort 1, levels of α-SMA were significantly higher in IPF, COPD and NSCLC patients compared to healthy controls (P = 0.04, P = 0.001 and P <0.0001, respectively). The area under the receiver operating characteristics (AUROC) for separation of healthy controls from IPF patients was 0.865, healthy controls from COPD patients was 0.892 and healthy controls from NSCLC patients was 0.983. In cohort 2, levels of α-SMA were also significantly higher in NSCLC patients compared to healthy controls (P = 0) and the AUROC for separating NSCLC and healthy controls was 0.715.

**CONCLUSIONS:** In this study we developed and validated a robust competitive ELISA assay targeting the N-terminal of α-SMA. The level of α-SMA was upregulated when adding TGF-β indicating that α-SMA is increased in activated fibroblasts. The level of α-SMA in circulation was significantly higher in patients with IPF, COPD and NSCLC compared to healthy controls. This assay could potentially be used as a novel noninvasive serological biomarker for lung disorders by providing a surrogate measure of activated fibroblasts.

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**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 on 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 13±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 did, however, compared with the refined grain diet, decrease 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.

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Personalized mathematical model of endotoxin-induced inflammatory responses in young men and associated changes in heart rate variability

The objective of this study was to develop a personalized inflammatory model and estimate subject-specific parameters that could be related to changes in heart rate variability (HRV), a measure that can be obtained non-invasively in real time. An inflammatory model was developed and calibrated to measurements of interleukin-6 (IL-6), tumor necrosis factor (TNF-alpha), interleukin-8 (IL-8) and interleukin-10 (IL-10) over 8 hours in 20 subjects administered a low dose of lipopolysaccharide. For this model, we estimated 11 subject-specific parameters for all 20 subjects. Estimated parameters were correlated with changes in HRV, computed from ECG measurements using a built-in HRV module available in Labchart. Results revealed that patients could be separated into two groups expressing normal and abnormal responses to endotoxin. Abnormal responders exhibited increased HRV, most likely as a result of increased vagal firing. The observed correlation between the inflammatory response and HRV brings us a step further towards understanding if HRV predictions can be used as a marker for inflammation. Analyzing HRV parameters provides an easy, non-invasively obtained measure that can be used to assess the state of the subject, potentially translating to identifying a non-invasive marker that can be used to detect the onset of sepsis.

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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.

A fragment of SPARC reflecting increased collagen affinity shows pathological relevance in lung cancer – implications of a new collagen chaperone function of SPARC

The matricellular protein SPARC (secreted proteome acidic and rich in cysteine) is known to bind collagens and regulate fibrillogenesis. Cleavage of SPARC at a single peptide bond, increases the affinity for collagens up to 20-fold. To investigate if this specific cleavage has pathological relevance in fibrotic disorders, we developed a competitive ELISA targeting the generated neo-epitope on the released fragment and quantified it in serum from patients with lung cancer, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and healthy subjects. Furthermore, the ability of SPARC to protect fibrillar collagens from proteolytic degradation was investigated in vitro, potentially adding a new collagen chaperone function to SPARC. The fragment was significantly elevated in lung cancer patients when compared to healthy subjects measured in a discovery cohort (p = 0.0005) and a validation cohort (p < 0.0001). No significant difference was observed for IPF and COPD patients compared to healthy subjects. When recombinant SPARC was incubated with type I or type III collagens and matrix metalloproteinase-9, collagen degradation was completely
inhibited. Together, these data suggest that cleavage of SPARC at a specific site, which modulates collagen binding, is a physiological mechanism increased during pathogenesis of lung cancer. Furthermore, inhibition of fibrillar collagen degradation by SPARC adds a new chaperone function to SPARC which may play additional roles in the contribution to increased collagen deposition leading to a pro-fibrotic and tumorigenic environment.

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**Age-related collagen turnover of the interstitial matrix and basement membrane: Implications of age- and sex-dependent remodeling of the extracellular matrix**

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.

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A novel biomarker of laminin turnover is associated with disease progression and mortality in chronic kidney disease

Background: Patients with chronic kidney disease (CKD) have increased risk of development of endstage renal disease (ESRD) and early mortality. Fibrosis is the central pathogenic process in CKD and is caused by dysregulated extracellular matrix (ECM) remodeling. The laminin γ1 chain (LAMC1) is a core structural protein present in the basement membrane of several organs, including the kidneys. We hypothesized that dysregulation of LAMC1 remodeling could be associated with a higher risk of adverse clinical outcomes in patients with CKD.

Methods: A novel immunoassay targeting LG1M, a specific MMP-9-generated neo-epitope fragment of LAMC1, was developed and used to measure the levels of the fragment in urine and serum from 492 patients from the Renal Impairment in Secondary Care (RIISC) study, a prospective cohort of patients with high-risk CKD. Patients were monitored for a median followup time of 3.5 years. Associations between serum and urine LG1M levels and progression of CKD at 12 months were assessed by a multivariable logistic regression model. The association with ESRD or mortality was assessed by Kaplan-Meier survival curves and Cox proportional hazards regression.

Results: Forty-six (11%) of the 416 patients who reached 12-month follow-up had progression of CKD; during the study follow-up, 125 patients (25.4%) developed ESRD and 71 patients (14.4%) died. Serum and urine levels of LG1M correlated with baseline eGFR (r = -0.43, p<0.0001 and r = -0.17, p = 0.0002, respectively). Serum levels of LG1M were higher in patients with one-year progression of CKD compared to those who did not progress (p<0.01). Baseline serum levels of LG1M were associated with development of ESRD (HR 3.2, 95% CI 1.99-5.2 for patients in the highest LG1M tertile compared to patient in the lowest tertile). Baseline urinary levels of LG1M (uLG1M) were significantly associated with mortality (HR 5.0, 95% CI 2.8-8.9, p<0.0001 for patients in the highest LG1M tertile compared to patients in the lowest tertile). Urine LG1M was retained in the model for prediction of mortality (HR per standard deviation of uLG1M: 1.01, 95% CI 1.00-1.02, p = 0.001).

Conclusions: LG1M, a marker of basement membrane remodeling, is increased in serum and urine of patients with CKD and levels are associated with one-year disease progression, development of ESRD, and mortality.
Division of Labor during Biofilm Matrix Production

Organisms as simple as bacteria can engage in complex collective actions, such as group motility and fruiting body formation. Some of these actions involve a division of labor, where phenotypically specialized clonal subpopulations or genetically distinct lineages cooperate with each other by performing complementary tasks. Here, we combine experimental and computational approaches to investigate potential benefits arising from division of labor during biofilm matrix production. We show that both phenotypic and genetic strategies for a division of labor can promote collective biofilm formation in the soil bacterium Bacillus subtilis. In this species, biofilm matrix consists of two major components, exopolysaccharides (EPSs) and TasA. We observed that clonal groups of B. subtilis phenotypically segregate into three subpopulations composed of matrix non-producers, EPS producers, and generalists, which produce both EPSs and TasA. This incomplete phenotypic specialization was outperformed by a genetic division of labor, where two mutants, engineered as specialists, complemented each other by exchanging EPSs and TasA. The relative fitness of the two mutants displayed a negative frequency dependence both in vitro and on plant roots, with strain frequency reaching a stable equilibrium at 30% TasA producers, corresponding exactly to the population composition where group productivity is maximized. Using individual-based modeling, we show that asymmetries in strain ratio can arise due to differences in the relative benefits that matrix compounds generate for the collective and that genetic division of labor can be favored when it breaks metabolic constraints associated with the simultaneous production of two matrix components. Microbes that live predominantly in complex biofilms often cooperate with each other by performing complementary tasks. DragoÅ¡ et al. use a plant-colonizing Bacillus subtilis model and combine experimental and computational approaches to demonstrate and rationalize benefits arising from genetic division of labor during biofilm matrix production.
Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis

Allergic rhinitis is the most common clinical presentation of allergy, affecting 400 million people worldwide, with increasing incidence in westernized countries. To elucidate the genetic architecture and understand the underlying disease mechanisms, we carried out a meta-analysis of allergic rhinitis in 59,762 cases and 152,358 controls of European ancestry and identified a total of 41 risk loci for allergic rhinitis, including 20 loci not previously associated with allergic rhinitis, which were confirmed in a replication phase of 60,720 cases and 618,527 controls. Functional annotation implicated genes involved in various immune pathways, and fine mapping of the HLA region suggested amino acid variants important for antigen binding. We further performed genome-wide association study (GWAS) analyses of allergic sensitization against inhalant allergens and nonallergic rhinitis, which suggested shared genetic mechanisms across rhinitis-related traits. Future studies of the identified loci and genes might identify novel targets for treatment and prevention of allergic rhinitis.
Integrative data analysis of genotype, microbiome and metabolomics for prediction of response to diet for improved metabolic health

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Markers of Basement Membrane Remodeling Are Associated With Higher Mortality in Patients With Known Atherosclerosis

**Background**
Patients with atherosclerosis have a high risk of cardiovascular events and death. Atherosclerosis is characterized by accumulation of lipids, cells and extracellular matrix proteins in the intima. We hypothesized that dysregulated remodeling of the basement membrane proteins may be associated with clinical outcomes in patients with atherosclerosis.

**Methods and Results**
Neoepitope fragments of collagen type IV (C4M) and laminin (LG1M) were assessed by ELISAs in serum from 787 endarterectomy patients. Matrix metalloproteinases were measured using proximity extension assay and correlated to C4M and LG1M levels using Spearman correlations. A total of 473 patients were followed up for 6 years using national registers, medical charts, and telephone interviews. The incidence of cardiovascular events, cardiovascular mortality, and all-cause mortality were associated to levels of C4M and LG1M using Kaplan–Meier curves and Cox regression analyses. A total of 101 patients had cardiovascular events, 39 died of cardiovascular mortality, and 64 patients died from all-cause mortality. C4M levels were increased in patients with symptomatic carotid atherosclerotic disease before surgery (P = 0.048). High C4M and LG1M levels were associated with increased risk of all-cause mortality (P=0.020 and 0.031, respectively) and predicted all-cause death together with glomerular filtration rate and diabetes mellitus.

**Conclusions**
High LG1M and C4M levels were associated with all-cause mortality, together with glomerular filtration rate and diabetes mellitus. These novel biomarkers need further evaluation but might be tools to identify high-risk patients.
Markers of basement membrane remodelling are associated with higher mortality in patients with advanced carotid atherosclerosis

Background: Patients with atherosclerosis have a known increased risk of cardiovascular events and early mortality. The atherosclerotic disease is characterized by accumulation of lipids, cells and proteins in the arterial wall, which includes remodelling of the extracellular matrix (ECM). Laminin and collagen type IV are the main ECM structural proteins present in the arterial basement membrane.

Microbial translocation revisited: targeting the endotoxic potential of gut microbes in HIV-infected individuals

OBJECTIVE: Translocation of microbial products such as lipopolysaccharides (LPS) from the gut may contribute to chronic inflammation in HIV-infected individuals. Recent studies indicate that differences in degree of acylation of gut-bacterial derived LPS may explain variable immune effects, with hexa-acylated rather than penta-acylated LPS having pro-inflammatory capacity. We investigated whether the degree of acylation of gut-derived LPS associates with systemic inflammation, and the potential effect of probiotic intervention. METHODS: Gut microbiota profiles from a probiotics intervention were investigated, and validated in a cohort of HIV-infected individuals commencing ART. The PICRUSt software was used to predict overall functional capacity of the microbiota, and in-house bioinformatics to distinguish between bacteria producing hexa- and penta-acylated LPS. RESULTS AND CONCLUSION: HIV-infected individuals with the highest ratio of pro-inflammatory hexa-acylated LPS- to non-inflammatory penta-acylated LPS-producing bacteria exhibited increased levels of systemic inflammation (neopterin, P<0.001) and tryptophan catabolism (kynurenine/tryptophan-ratio, P=0.01), indicating a link between pro-inflammatory LPS, tryptophan catabolism and inflammation. After probiotics for eight weeks, there was a decrease in gram-negative bacteria (P=0.01), related primarily to a reduction in bacteria producing penta-acylated LPS (P=0.01), but not hexa-acylated LPS. The reduction in gram-negative bacteria correlated positively with decreased plasma LPS (r=0.72), mainly related to a reduction in bacteria producing non-inflammatory penta-acylated LPS (r=0.58). Notably, gut bacteria producing hexa-acylated LPS were outnumbered by penta-acylated LPS with a factor of 25 in HIV-infected individuals. Further studies are warranted to determine whether microbes producing hexa-acylated LPS might be a more relevant trigger of systemic inflammation compared to plasma LPS captured by the existing limulus assay.
Neonates colonized with pathogenic bacteria in the airways have a low-grade systemic inflammation

Background and Objectives: The development of childhood asthma is associated with neonatal colonization with pathogenic bacteria in hypopharynx. Furthermore, established asthma is associated with systemic low-grade inflammation. We here report on the association between neonatal colonization with pathogenic bacteria in hypopharynx and the development of systemic low-grade inflammation. Methods: Bacterial colonization of the hypopharynx with *M. catharralis, H. influenzae* and/or *S. pneumoniae* was assessed in asymptomatic children from the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) cohort at age 1 month by culturing technique (N=238) and by quantitative polymerase chain reaction (qPCR) technique (N=249) and in the COPSAC cohort by culturing at age 1 month (N=622) and again at age 3 months (N=613). Systemic low-grade inflammation was determined in both cohorts at age 6 months by measuring plasma levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6). Results: In both cohorts, bacterial colonization was associated with increased levels of hs-CRP: COPSAC2000, 1 month culturing (geometric mean ratio of colonized/non-colonized [95% CI]), 1.39 [0.97-2.01], p=0.08, 1 month qPCR, 1.55 [1.14-2.10], p<0.01. A multi-parametric principal component analysis incorporating hs-CRP, TNF-α and IL-6 confirmed a systemic inflammatory profile in children colonized with *M. catharralis, H. influenzae* and/or *S. pneumoniae* in the hypopharynx compared to non-colonized children (p-values<0.05). Conclusion: The composition of the upper airway microbiome in early life may cause systemic low-grade inflammation.

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.

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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.

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The metagenome of the female upper reproductive tract

Background: The human uterus is traditionally believed to be sterile, while the vaginal microbiota plays an important role in fending off pathogens. Emerging evidence demonstrates the presence of bacteria beyond the vagina. However, a microbiome-wide metagenomic analysis identifying the overall microorganism communities has been lacking.

Results: We performed shotgun-sequencing using the Illumina platform of 52 samples from the cervical canal and peritoneal fluid of Chinese women in reproductive age. Direct annotation of sequencing reads identified the taxonomy of bacteria, archaea, fungi and viruses, confirming and extending the results from our previous study. We replicated the findings in another 24 samples from the vagina, the cervical canal, the uterus and peritoneal fluid using BGISEQ-500 platform, revealing that microorganisms in the samples from the same individual were largely shared in the whole reproductive tract. Over 99% human sequences were detected in the 20GB raw data. After filtering, vaginal microorganisms were well covered in the generated reproductive tract gene catalogue, while the more diverse upper reproductive tract microbiota might need greater depth of sequencing and more samples to meet the full coverage scale.

Conclusions: Microbiota in unprecedented data for uncharted body site, female upper reproductive tract, were analyzed in this study. The community results indicated that an intra-individual continuum of all types of microorganisms gradually changed from the vagina to the peritoneal fluid. A framework was also established in this study aiming at understanding the implications of the composition and functional potential of this distinct microbial ecosystem in relation to health and disease.

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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 0.73. 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.

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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.
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.
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.
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.
see the research article "Mucin- and carbohydrate-stimulated adhesion and subproteome changes of the probiotic bacterium Lactobacillus acidophilus NCFM" (Celebioglu et al., 2017) [1].

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**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 reestablish 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 2a, 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.

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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.

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Metabolic Syndrome, Insulin Resistance and Cognitive Dysfunction: Does your metabolic profile affect your brain?
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.

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.
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, 3OS 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-digestible 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 synbiotic interactions, including stimulation of adhesion.
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.

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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.

**General information**

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Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2018 › Research › peer-review

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
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.

General information
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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, BGI-Shenzhen, Guangdong Cardiovascular Institute, Chinese PLA General Hospital, Peking Union Medical College, Shanghai Jiao Tong University
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Source: FindIt
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.

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Organisations: Department of Biotechnology and Biomedicine, Disease Systems Immunology, Deakin University, University of Sydney, Murdoch Children's Research Institute
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Source: FindIt
Source-ID: 2392139022
Research output: Contribution to journal › Journal article – Annual report year: 2017 › Research › peer-review

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.

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

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.

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Research output: Contribution to journal › Journal article – Annual report year: 2017 › Research › peer-review

Weight Change and Risk of Hyperglycaemia 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\geq5.6 \text{ mmol/L} or HbA1c\geq42 \text{ mmol/mol}) in normalweight (BMI\leq25 \text{ kg/m2}), overweight (BMI=25–29.9 \text{ kg/m2}) and obese (BMI\geq30 \text{ 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.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Department of Biotechnology and Biomedicine, Disease Systems Immunology, Nordic Bioscience A/S, Odense University Hospital
Contributors: Møller, K. D., Neergaard, J., Christiansen, C., Karsdal, M. A., Beck-Nielsen, H., Pedersen, S. B., Henriksen, K.
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Source-ID: 133863900
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Delivery of TLR7 agonist to monocytes and dendritic cells by DCIR targeted liposomes induces robust production of anti-cancer cytokines.

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CRS_202016_Poster_TK.pdf
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Differential proteome and cellular adhesion analyses of the probiotic bacterium Lactobacillus acidophilus NCFM grown on raffinose - an emerging prebiotic
Whole cell and surface proteomes were analyzed together with adhesive properties of the probiotic bacterium Lactobacillus acidophilus NCFM (NCFM) grown on the emerging prebiotic raffinose, exemplifying a symbiotic. Adhesion of NCFM to mucin and intestinal HT-29 cells increased three-fold after culture with raffinose versus glucose, as also visualized by scanning electron microscopy. Comparative proteomics using 2D-DIGE showed 43 unique proteins to change in relative abundance in whole cell lysates from NCFM grown on raffinose compared to glucose. Furthermore, 14 unique proteins in 18 spots of the surface subproteome underwent changes identified by differential 2DE, including elongation factor G, thermostable pullulanase, and phosphate starvation inducible stress-related protein increasing in a range of +2.1 − +4.7 fold. By contrast five known moonlighting proteins decreased in relative abundance by up to −2.4 fold. Enzymes involved in raffinose catabolism were elevated in the whole cell proteome; α-galactosidase (+13.9 fold);
sucrose phosphorylase (+5.4 fold) together with metabolic enzymes from the Leloir pathway for galactose utilization and the glycolysis; β-galactosidase (+5.7 fold); galactose (+2.9/+3.1 fold) and fructose (+2.8 fold) kinases. The insights at the molecular and cellular levels contributed to the understanding of the interplay of a synbiotic composed of NCFM and raffinose with the host.

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Scopus rating (2016): CiteScore 3.85 SJR 1.564 SNIP 0.889
Web of Science (2016): Impact factor 4.041
Web of Science (2016): Indexed yes
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Research output: Contribution to journal › Journal article – Annual report year: 2016 › Research › peer-review

Divergent Response Profile in Activated Cord Blood T cells from First-born Child Implies Birth-order-associated in Utero Immune Programming

Background: First-born children are at higher risk for development of a range of immune-mediated diseases. The underlying mechanism of ‘birth-order-effects’ on disease risk is largely unknown, but in utero programming of the child’s immune system may play a role. **Objective:** We studied the association between birth-order and the functional response of stimulated cord blood T cells. **Method:** Purified cord blood T cells were polyclonally activated with anti-CD3/CD28-coated beads in a subgroup of 28 children enrolled in the COPSAC2010 birth cohort. Expression levels of seven activation markers on helper and cytotoxic T cells as well as the percentage of CD4+CD25+ T cells were assessed by flow cytometry. Production of IFN-γ, TNF-α, IL-17, IL-4, IL-5, IL-13 and IL-10 was measured in supernatants. **Results:** IL-10 secretion (P = 0.007) and CD25 expression on CD4+ helper T cells (P = 0.0003) in activated cord blood T cells were selectively reduced in first-born children, while the percentage of CD4+CD25+ cord blood T cells was independent of birth-order. **Conclusion:** First-born infants display a reduced anti-inflammatory profile in T cells at birth. This possible in utero ‘birth-order’ T cell programing may contribute to later development of immune-mediated diseases by increasing overall immune reactivity in first-born children as compared to younger siblings.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
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Ratings:
Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomised clinical trial

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Copenhagen University Hospital, Aarhus University Hospital, University of Copenhagen
Contributors: Chawes, B., Bonnelykke, K., Stokholm, J., Heickendorff, L., Pedersen, S. B., Rasmussen, M., Bisgaard, H.
Number of pages: 1
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Web of Science (2016): Indexed yes
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**Effect of Vitamin D$_3$ Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring A Randomized Clinical Trial: A Randomized Clinical Trial**

**IMPORTANCE:** Observational studies have suggested that increased dietary vitamin D intake during pregnancy may protect against wheezing in the offspring, but the preventive effect of vitamin D supplementation to pregnant women is unknown. **OBJECTIVE:** To determine whether supplementation of vitamin D$_3$ during the third trimester of pregnancy reduces the risk of persistent wheeze in the offspring. **DESIGN, SETTING, AND PARTICIPANTS:** A double-blind, single-center, randomized clinical trial conducted within the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort. Enrollment began March 2009 with a goal of 708 participants, but due to delayed ethical approval, only 623 women were recruited at 24 weeks of pregnancy. Follow-up of the children (N = 581) was completed when the youngest child reached age 3 years in March 2014. **INTERVENTIONS** Vitamin D$_3$ (2400 IU/d; n = 315) or matching placebo tablets (n = 308) from pregnancy week 24 to 1 week postpartum. All women received 400 IU/d of vitamin D$_3$ as part of usual pregnancy care. **MAIN OUTCOMES AND MEASURES:** Age at onset of persistent wheeze in the first 3 years of life. Secondary outcomes included number of episodes of troublesome lung symptoms, asthma, respiratory tract infections, and neonatal airway immunology. **ADVERSE EVENTS** were assessed. **RESULTS:** Of the 581 children, persistent wheeze was diagnosed during the first 3 years of life in 47 children (16%) in the vitamin D$_3$ group and 57 children (20%) in the control group. Vitamin D$_3$ supplementation was not associated with the risk of persistent wheeze, but the number of episodes of troublesome lung symptoms was reduced, and the airway immune profile was up-regulated (principal component analysis, P=.04). There was no effect on additional end points. **CONCLUSIONS AND RELEVANCE:** The use of 2800 IU/d of vitamin D$_3$ during the
third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years. However, interpretation of the study is limited by a wide CI that includes a clinically important protective effect.

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- ISSN (Print): 0098-7484
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  - Web of Science (2016): Impact factor 44.405
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Excessive collagen turnover products are released during colorectal cancer progression and elevated in serum from metastatic colorectal cancer patients

During cancer progression, the homeostasis of the extracellular matrix becomes imbalanced with an excessive collagen remodeling by matrix metalloproteinases. As a consequence, small protein fragments of degraded collagen are released into the circulation. We have investigated the potential of protein fragments of collagen type I, III and IV as novel biomarkers for colorectal cancer. Specific fragments of degraded type I, III and IV collagen (C1M, C3M, C4M) and type III collagen formation (Pro-C3) were assessed in serum from colorectal cancer patients, subjects with adenomas and matched healthy controls using well-characterized and validated ELISAs. Serum levels of the biomarkers were significantly elevated in colorectal cancer patients compared to subjects with adenomas (C1M, Pro-C3, C3M) and controls (C1M, Pro-C3). When patients were stratified according to their tumour stage, all four biomarkers were able to differentiate stage IV metastatic patients from all other stages. Combination of all markers with age and gender in a logistic regression model discriminated between metastatic and non-metastatic patients with an AUROC of 0.80. The data suggest that the levels of these collagen remodeling biomarkers may be a measure of tumour activity and invasiveness and may provide new clinical tools for monitoring of patients with advanced stage colorectal cancer.

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- Contributors: Kehlet, S. N., Sanz-Pamplona, R., Pedersen, S. B., Leeming, D., Karsdal, M. A., Moreno, V.
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- Ratings:
  - BFI (2016): BFI-level 1
High breast milk IL-1β level is associated with reduced risk of childhood eczema

We recently demonstrated a dual effect of breastfeeding with increased risk of eczema and decreased risk of wheezing in early childhood by increasing breastfeeding length. We hypothesize that immune mediators in breast milk could explain such association either through a direct effect or as a surrogate marker of maternal immune constitution.

Human gut microbes impact host serum metabolome and insulin sensitivity

Insulin resistance is a forerunner state of ischaemic cardiovascular disease and type 2 diabetes. Here we show how the human gut microbiome impacts the serum metabolome and associates with insulin resistance in 277 non-diabetic Danish individuals. The serum metabolome of insulin-resistant individuals is characterized by increased levels of branched-chain amino acids (BCAAs), which correlate with a gut microbiome that has an enriched biosynthetic potential for BCAAs and is deprived of genes encoding bacterial inward transporters for these amino acids. Prevotella copri and Bacteroides vulgatus are identified as the main species driving the association between biosynthesis of BCAAs and insulin resistance, and in mice we demonstrate that P. copri can induce insulin resistance, aggravate glucose intolerance and augment circulating levels of BCAAs. Our findings suggest that microbial targets may have the potential to diminish insulin resistance and reduce the incidence of common metabolic and cardiovascular disorders.
Identification of differentially IgA-coated bacteria in inflammation-induced colorectal cancer

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Contributors: Eriksen, C., Holm, J. B., Yassin, M., Olsen, J., Pedersen, A. E., Kristiansen, K., Brix, S.
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Metabolic syndrome and subsequent risk of type 2 diabetes and cardiovascular disease in elderly women Challenging the current definition: Challenging the current definition

The prognostic value of the metabolic syndrome (MetS) is believed to vary with age. With an elderly population expecting to triple by 2060, it is important to evaluate the validity of MetS in this age group. We examined the association of MetS risk factors with later risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD) in elderly Caucasian women. We further investigated if stratification of individuals not defined with MetS would add predictive power in defining future disease prevalence of individuals with MetS. The Prospective Epidemiological Risk Factor Study, a community-based cohort study, followed 3905 Danish women since 2000 (age: 70.1±6.5) with no previous diagnosis of T2DM or CVD, holding all measurements used for MetS definition; central obesity, hypertension, hyperlipidemia, and hyperglycemia combined with register-based follow-up information. Elderly women with defined MetS presented a 6.3-fold increased risk of T2DM (95% confidence interval: [3.74-10.50]) and 1.7-fold increased risk of CVD (1.44-2.05) compared to women with no MetS risk factors. Subdividing the control group without defined MetS revealed that both centrally obese controls and controls holding other MetS risk factors also had increased risk of T2DM (hazard ratio (HR)=2.21 [1.25-3.93] and HR=1.75 [1.04-2.96]) and CVD (HR=1.51 [1.25-1.83] and HR=1.36 [1.15-1.60]) when compared to controls with no MetS risk factors. MetS in elderly Caucasian women increased risk of future T2DM and CVD. While not defined with MetS, women
Pan-HER - an antibody mixture targeting EGFR, HER2, and HER3 abrogates preformed and ligand-induced EGFR homo- and heterodimers: Pan-HER abrogates EGFR dimers

The human epidermal growth factor receptor (HER)-family is involved in development of many epithelial cancers. Therefore, HER-family members constitute important targets for anti-cancer therapeutics such as monoclonal antibodies (mAbs). A limitation to the success of single HER-targeting mAbs is development of acquired resistance through mechanisms such as altered receptor dimerization patterns and dependencies. Pan-HER is a mixture of six mAbs simultaneously targeting epidermal growth factor receptor (EGFR), HER2, and HER3 with two mAbs against each receptor. Pan-HER has previously demonstrated broader efficacy than targeting single or dual receptor combinations also in resistant settings. In light of this broad efficacy, we decided to investigate the effect of Pan-HER compared with single HER-targeting with single and dual mAbs on HER-family cross-talk and dimerization focusing on EGFR. The effect of Pan-HER on cell proliferation and HER-family receptor degradation was superior to treatment with single mAbs targeting either single receptor, and similar to targeting a single receptor with two non-overlapping antibodies. Furthermore, changes in EGFR-dimerization patterns after treatment with Pan-HER were investigated by in situ proximity ligation assay and co-immunoprecipitation, demonstrating that Pan-HER and the EGFR-targeting mAb mixture efficiently down-regulate basal EGFR homo- and heterodimerization in two tested cell lines, whereas single mAbs had limited effects. Pan-HER and the EGFR-targeting mAb mixture also blocked EGF-binding and thereby ligand-induced changes in EGFR-dimerization levels. These results suggest that Pan-HER reduces the cellular capability to switch HER-dependency and dimerization pattern in response to treatment and thus hold promise for future clinical development of Pan-HER in resistant settings. This article is protected by copyright. All rights reserved.
Picornavirus-Induced Airway Mucosa Immune Profile in Asymptomatic Neonates

Bacterial airway colonization is known to alter the airway mucosa immune response in neonates whereas the impact of viruses is unknown. The objective was therefore to examine the effect of respiratory viruses on the immune signature in the airways of asymptomatic neonates. Nasal aspirates from 571 asymptomatic 1-month-old neonates from the Copenhagen Prospective Studies on Asthma in Childhood 2010 birth cohort were investigated for respiratory viruses. Simultaneously, unstimulated airway mucosal lining fluid was obtained and quantified for levels of 20 immune mediators related to type 1, type 2, type 17, and regulatory immune paths. The association between immune mediator levels and viruses was tested by conventional statistics and partial least square discriminant analysis. Picornaviruses were detected in 58 neonates (10.2%) and other viruses in 10 (1.8%). A general up-regulation of immune mediators was found in the neonates with picornavirus (P <.0001; partial least square discriminant analysis). The association was pronounced for type 1- and type 2-related markers and was unaffected by comprehensive confounder adjustment. Detection of picornavirus and bacteria was associated with an additive general up-regulating effect. Asymptomatic presence of picornavirus in the neonatal airway is a potent activator of the topical immune response. This is relevant to understanding the immune potententiating effect of early life exposure to viruses.

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Web of Science (2016): Indexed yes
Original language: English
Season of birth shapes neonatal immune function

Birth season has been reported to be a risk factor for several immune-mediated diseases. We hypothesized that this association is mediated by differential changes in neonatal immune phenotype and function with birth season. We sought to investigate the influence of season of birth on cord blood immune cell subsets and inflammatory mediators in neonatal airways. Cord blood was phenotyped for 26 different immune cell subsets, and at 1 month of age, 20 cytokines and chemokines were quantified in airway mucosal lining fluid. Multivariate partial least squares discriminant analyses were applied to determine whether certain immune profiles dominate by birth season, and correlations between individual cord blood immune cells and early airway immune mediators were defined. We found a birth season-related fluctuation in neonatal immune cell subsets and in early-life airway mucosal immune function. The seasonal airway immune pattern was associated with the number of activated and regulatory T cells in cord blood whereas it was independent of concomitant presence of pathogenic airway microbes. Specifically, summer newborns presented with the lowest levels of all cell types and mediators; fall newborns displayed high levels of activated T cells and mucosal IL-12p70, TNF-α, IL-13, IL-10, and IL-2; and winter newborns had the highest levels of innate immune cells, IL-5, type 17-related immune mediators, and activated T cells. Birth season fluctuations seem to affect neonatal immune development and result in differential potentiation of cord blood immune cells and early airway mucosal immune function.

General information

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Siblings Promote a Type 1/Type 17-oriented immune response in the airways of asymptomatic neonates

BACKGROUND: Siblings have been shown to reduce the risk of later asthma and allergy, but the mechanism driving this association is unknown. The objective was to study whether siblings affect the airway immune response in healthy neonates. We hypothesized that siblings exert immune modulatory effects on neonates mirrored in the airway mucosa.

METHODS: We measured 20 immune-mediators related to the Type 1, Type 2, Type 17 or regulatory immune pathways in the airway mucosa of 571 one-month-old asymptomatic neonates from the Copenhagen Prospective Studies on Asthma in Childhood birth-cohort (COPSAC2010). The association between airway mediator levels and presence of siblings was investigated using conventional statistics and principle component analyses (PCA). RESULTS: Neonates with siblings had an up-regulated level of airway immune-mediators, with predominance of Type 1- and Type 17-related mediators. This was supported by the PCA showing a highly significant difference between children with vs. without siblings: p<10^{-10}, which persisted after adjustment for potential confounders including pathogenic airway bacteria and viruses: p<0.0001.
The immune priming effect was inversely associated with time since last childbirth: \( p=0.0015 \). CONCLUSIONS: Siblings mediate a Type 1/Type 17-related immune-stimulatory effect in the airways of asymptomatic neonates, also after adjustment for pathogenic bacteria and viruses, indicating that siblings exert a transferable early immune modulatory effect. These findings may represent an *in-utero* immune priming effect of the fetal immune system caused by previous pregnancies as the effect was attenuated with time since last childbirth or presence of unidentified microbes, but further studies are needed to confirm our findings.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Contributors: Wolsk, H. M., Chawes, B. L., Falsgaard, N. V., Rasmussen, M. A., Pedersen, S. B., Bisgaard, H. F.
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Research output: Contribution to journal › Journal article – Annual report year: 2016 › Research › peer-review

**Susceptibility to Lower Respiratory Infections in Childhood is Associated with Perturbation of the Cytokine Response to Pathogenic Airway Bacteria**
BACKGROUND: Neonatal colonization of the airways with respiratory pathogens is associated with increased risk of lower respiratory infections (LRI) in early childhood. Therefore, we hypothesized that children developing LRI have an aberrant immune response to pathogenic bacteria in infancy. OBJECTIVE: To characterize in vitro the early life systemic immune response to pathogenic bacteria and study the possible association with incidence of LRI during the first 3 years of life. METHODS: The Copenhagen Prospective Study on Asthma in Childhood2000 (COPSAC2000) is a clinical birth cohort study of 411 children born of mothers with asthma. LRI incidence was prospectively captured from 6-monthly planned visits and visits at acute respiratory episodes. The in vitro systemic immune response to H. influenzae, M. catarrhalis and S. pneumoniae was characterized by the production of TNF-α, IFN-γ, IL-2, IL-5, IL-10, IL-13, and IL-17 in peripheral blood mononuclear cells isolated at age 6 months from 291 infants. Data were analyzed by Poisson regression against incidence of LRI in infancy. RESULTS: A multivariable model including all cytokine responses from the three different bacterial stimulations significantly identified children at risk of LRI (\( p=0.006 \)). The immune response pattern associated with LRI was characterized by perturbed production of several cytokines rather than production of one specific cytokine, and was independent of concurrent asthma. TNF-α and IL-5 were key drivers but did not explain the entire variation in LRI susceptibility. CONCLUSIONS: Children at risk of future LRI present a perturbed systemic immune response upon exposure to common airway pathogens in early life.

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Targeting the DCIR Receptor with a TLR7 Agonist Specifically Activates Monocytes and DCs

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Airway Mucosal Immune-suppression in Neonates of Mothers Receiving A(H1N1)pnd09 Vaccination During Pregnancy

Background: It is recommended to vaccinate pregnant women against influenza. A possible impact on the immune expression of the fetus has never been studied. We aim to study the immune signature in the upper airways and the incidence of infections in neonates born to mothers receiving Influenza A(H1N1) pnd09 vaccination during pregnancy.

Methods: One hundred and fifty-six women from the unselected Copenhagen Prospective Study on Asthma in Childhood (COPSAC 2010) received Influenza A(H1N1) pnd09-vaccination during the 2009 pandemic. Fifty-one mothers received the vaccine during pregnancy and 105 after pregnancy; 332 neonates of nonvaccinated mothers were included as secondary controls. Nasal mucosal lining fluid was sampled in 488 neonates and assessed for interleukin (IL)-12p70, IP-10, interferon-gamma (IFN)-gamma, tumor necrosis factor-alpha (TNF)-alpha, MIP-1 beta, MCP-1, MCP-4, IL-4, IL-5, IL-13, eotaxin-1, eotaxin-3, TARC, MDC, IL-17, IL-1 beta, IL-8, transforming growth factor beta (TGF)-beta 1, IL-10 and IL-2. Infections were monitored the first year of life by daily diary cards and clinical controls.

Results: Neonates of mothers vaccinated during pregnancy had significant up-regulation of TGF-beta 1 [ratio = 1.52 (1.22-1.90), P = 0.0002], and corresponding down-regulation (P <0.05) of IL-12p70, IFN-gamma, IL-5, eotaxin-1, TARC, MDC, IL-17, IL-1 beta, IL-8, transforming growth factor beta (TGF)-beta 1, IL-10 and IL-2. Infections were monitored the first year of life by daily diary cards and clinical controls. Results: Neonates of mothers vaccinated during pregnancy had significant up-regulation of TGF-beta 1 [ratio = 1.52 (1.22-1.90), P = 0.0002], and corresponding down-regulation (P <0.05) of IL-12p70, IFN-gamma, IL-5, eotaxin-1, TARC, MDC, IL-8 in comparison to those vaccinated after pregnancy. The lag-time from vaccination during pregnancy to assessment of the immune signature showed significant and positive association to up-regulation of TGF-beta 1 levels (P = 0.0003) and significant negative association to other mediators. The study was not powered to study differences in the incidence of infections in early infancy which did not differ between the study groups. Conclusion: Influenza A(H1N1) pnd09 vaccination during pregnancy up-regulates TGF-beta 1 and down-regulates key mediators of the protective immunity.

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Publication information
Allergic sensitization at school age is a systemic low-grade inflammatory disorder
Systemic low-grade inflammation has been demonstrated in a range of the frequent noncommunicable diseases (NCDs) as a possible shared mechanism, but is largely unexplored in relation to allergic sensitization. Therefore, we aimed to investigate the possible association between systemic low-grade inflammation and childhood allergic sensitization.

Breast milk IL-1β level associates with development of eczema during early childhood
We recently demonstrated a dual effect of breastfeeding with increased risk of eczema and decreased risk of wheezing in early childhood. We hypothesized that maternal immune constitution characterized by breast milk mediators may explain such association.
Chronic obstructive pulmonary disease and asthma-associated Proteobacteria, but not commensal Prevotella spp., promote Toll-like receptor 2-independent lung inflammation and pathology

Recent studies of healthy human airways have revealed colonization by a distinct commensal bacterial microbiota containing Gram-negative Prevotella spp. However, the immunological properties of these bacteria in the respiratory system remain unknown. Here we compare the innate respiratory immune response to three Gram-negative commensal Prevotella strains (Prevotella melaninogenica, Prevotella nanceiensis and Prevotella salivae) and three Gram-negative pathogenic Proteobacteria known to colonize lungs of patients with chronic obstructive pulmonary disease (COPD) and asthma (Haemophilus influenzae B, non-typeable Haemophilus influenzae and Moraxella catarrhalis). The commensal Prevotella spp. and pathogenic Proteobacteria were found to exhibit intrinsic differences in innate inflammatory capacities on murine lung cells in vitro. In vivo in mice, non-typeable H.influenzae induced severe Toll-like receptor 2 (TLR2)-independent COPD-like inflammation characterized by predominant airway neutrophilia, expression of a neutrophilic cytokine/chemokine profile in lung tissue, and lung immunopathology. In comparison, P.nanceiensis induced a diminished neutrophilic airway inflammation and no detectable lung pathology. Interestingly, the inflammatory airway response to the Gram-negative bacteria P.nanceiensis was completely TLR2-dependent. These findings demonstrate weak inflammatory properties of Gram-negative airway commensal Prevotella spp. that may make colonization by these bacteria tolerable by the respiratory immune system.

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Contributors: Larsen, J. M., Musavian, H. S., Butt, T. M., Ingvorsen, C., Thysen, A. H., Brix, S.
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Distinct inflammatory and cytopathic characteristics of *Escherichia coli* isolates from inflammatory bowel disease patients

*Escherichia coli* (*E. coli*) may be implicated in the pathogenesis of inflammatory bowel disease (IBD), as implied from a higher prevalence of mucosa-associated *E. coli* in the gut of IBD-affected individuals. However, it is unclear whether different non-diarrheagenic *E. coli* spp. segregate from each other in their ability to promote intestinal inflammation. Herein we compared the inflammation-inducing properties of non-diarrheagenic LF82, 691-04A, *E. coli* Nissle 1917 (ECN) and eleven new intestinal isolates from different locations in five IBD patients and one healthy control. Viable *E. coli* were cultured with human monocyte-derived dendritic cells (moDCs) and monolayers of intestinal epithelial cells (IECs), followed by analysis of secreted cytokines, intracellular levels of reactive oxygen species and cellular death. The IBD-associated *E. coli* LF82 induced the same dose-dependent inflammatory cytokine profile as ECN and ten of the new *E. coli* isolates displayed as high level IL-12p70, IL-1β, IL-23 and TNF-α from moDCs irrespective of their site of isolation (ileum/colon/faeces), disease origin (diseased/non-diseased) or known virulence factors. Contrarily, 691-04A and one new IBD *E. coli* isolate induced a different cellular phenotype with enhanced killing of moDCs and IECs, coupled to elevated IL-18. The cytopathic nature of 691-04A and one other IBD *E. coli* isolate suggests that colonization with specific non-diarrheagenic *E. coli* could promote intestinal barrier leakage and profound intestinal inflammation, while LF82, ECN and the remaining non-diarrheagenic *E. coli* isolates hold notorious pro-inflammatory characteristics that can progress inflammation in case of intestinal barrier leakage.

Gliadin affects glucose homeostasis and intestinal metagenome in C57BL6 mice fed a high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse.

Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S
rRNA genes showed that gliadin altered the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. Moreover, gliadin reduced the ileal gene expression of tight junction protein 1, occludin, cadherin 1, mucin 2 and mucin 3, indicating an impaired intestinal barrier function. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10).

Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the intestinal microbiota composition. Comprehensive analyses of metabolites, histological sections and the profile of specific immune cells are in progress to elucidate the mechanism behind the observed effects.

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Gliadin intake alters intestinal microbiota, glucose and lipid metabolism, and adipose tissue and liver immune cells

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Inflammatory Mediator Profiling of n-butanol Exposed Upper Airways in Individuals with Multiple Chemical Sensitivity
Multiple Chemical Sensitivity (MCS) is a chronic condition characterized by reports of recurrent symptoms in response to low level exposure to various chemical substances. Recent findings suggest that dysregulation of the immune system may play a role in MCS pathophysiology. The aim of this study was to examine baseline and low dose n-butanol-induced upper airway inflammatory response profiles in MCS subjects versus healthy controls. Eighteen participants with MCS and 18 age- and sex-matched healthy controls were enrolled in the study. Epithelial lining fluid was collected from the nasal cavity at three time points: baseline, within 15 minutes after being exposed to 3.7 ppm n-butanol in an exposure chamber and four hours after exposure termination. A total of 19 cytokines and chemokines were quantified. Furthermore, at
baseline and during the exposure session, participants rated the perceived intensity, valence and levels of symptoms and autonomic recordings were obtained. The physiological and psychophysical measurements during the n-butanol exposure session verified a specific response in MCS individuals only. However, MCS subjects and healthy controls displayed similar upper airway inflammatory mediator profiles (P>0.05) at baseline. Likewise, direct comparison of mediator levels in the MCS group and controls after n-butanol exposure revealed no significant group differences. We demonstrate no abnormal upper airway inflammatory mediator levels in MCS subjects before or after a symptom-eliciting exposure to low dose n-butanol, implying that upper airways of MCS subjects are functionally intact at the level of cytokine and chemokine production and secretory capacity. This suggests that previous findings of increased cytokine plasma levels in MCS are unlikely to be caused by systemic priming via excessive upper airway inflammatory processes.

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Capital Region of Denmark, Umeå University

Contributors: Dantoft, T. M., Skovbjerg, S., Andersson, L., Claeson, A., Lind, N., Nordin, S., Pedersen, S. B.

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Research output: Contribution to journal › Journal article – Annual report year: 2015 › Research › peer-review

**Maternal fatty acid desaturase genotype correlates with infant immune responses at 6 months**

Breast milk long-chain PUFA (LCPUFA) have been associated with changes in early life immune responses and may modulate T-cell function in infancy. We studied the effect of maternal fatty acid desaturase (FADS) genotype and breast milk LCPUFA levels on infants’ blood T-cell profiles and ex vivo-produced cytokines after anti-CD3/CD28 stimulation of peripheral blood mononuclear cells in 6-month-old infants from the Copenhagen Prospective Study of Asthma in Childhood birth cohort. LCPUFA concentrations of breast milk were assessed at 4 weeks of age, and FADS SNP were determined in both mothers and infants (n 109). In general, breast milk arachidonic acid (AA) levels were inversely correlated with the production of IL-10 (r = -0.25; P=0.004), IL-17 (r = -0.24; P=0.005), IL-5 (r = -0.21; P=0.014) and IL-13 (r = -0.17; P=0.047), whereas EPA was positively correlated with the counts of blood regulatory T-cells and cytotoxic T-cells and decreased T-helper cell counts. The minor FADS alleles were associated with lower breast milk AA and EPA, and infants of mothers carrying the minor allele of FADS SNP rs174556 had higher production of IL-10 (r = -0.23; P=0.018), IL-17 (r = -0.25; P=0.009) and IL-5 (r = -0.21; P=0.038) from ex vivo-activated immune cells. We observed no association between T-cell distribution and maternal or infant FADS gene variants. We conclude that increased maternal LCPUFA synthesis and breast milk AA are associated with decreased levels of IL-5, IL-13 (type-2 related), IL-17 (type-17 related) and IL-10 (regulatory immune responses), but not with interferon-γ and TNF-α, which could be due to an effect of the maternal FADS variants on the offspring immune response transferred via breast milk LCPUFA. Copyright © The Authors 2015.

**General information**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Systems Biology of Immune Regulation, University of Copenhagen
Metagenomic heterogeneity explains dual immune effects of endotoxins

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Systems Biology of Immune Regulation, Copenhagen University Hospital
Contributors: Pedersen, S. B., Eriksen, C., Larsen, J. M., Bisgaard, H. F.
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Neonates with reduced neonatal lung function have systemic low-grade inflammation

Background: Children and adults with asthma and impaired lung function have been reported to have low-grade systemic inflammation, but it is unknown whether this inflammation starts before symptoms and in particular whether low-grade inflammation is present in asymptomatic neonates with reduced lung function. Objective We sought to investigate the possible association between neonatal lung function and biomarkers of systemic inflammation. Methods: Plasma levels of high-sensitivity C-reactive protein (hs-CRP), IL-1β, IL-6, TNF-α, and CXCL8 (IL-8) were measured at age 6 months in 300 children of the Copenhagen Prospective Study on Asthma in Childhood birth cohort who had completed neonatal lung function testing at age 4 weeks. Associations between neonatal lung function
indices and inflammatory biomarkers were investigated by conventional statistics and unsupervised principal component analysis.

Results: The neonatal forced expiratory volume at 0.5 seconds was inversely associated with hs-CRP (β-coefficient, −0.12; 95% CI, −0.21 to −0.04; P <.01) and IL-6 (β-coefficient, −0.10; 95% CI, −0.18 to −0.01; P = .03) levels. The multivariate principal component analysis approach, including hs-CRP, IL-6, TNF-α, and CXCL8, confirmed a uniform upregulated inflammatory profile in children with reduced forced expiratory volume at 0.5 seconds (P = .02). Adjusting for body mass index at birth, maternal smoking, older children in the home, neonatal bacterial airway colonization, infections 14 days before, and asthmatic symptoms, as well as virus-induced wheezing, at any time before biomarker assessment at age 6 months did not affect the associations. Conclusion: Diminished neonatal lung function is associated with upregulated systemic inflammatory markers, such as hs-CRP.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
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Prelabor cesarean section bypasses natural immune cell maturation

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Shared genetic origins of allergy and autoimmune diseases
Parallel increases in allergy and autoimmune disease prevalence in recent time suggest shared, but yet unknown, etiologies. Here, we investigated shared genetic loci and molecular pathways to identify possible shared disease mechanisms between allergy and autoimmune diseases.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Helmholtz Zentrum München, Imperial College London, University of Queensland, University of Groningen, Boston Children's Hospital, Busselton Population Medical Research Foundation, University of Manchester, 23andMe Inc., University of Western Australia, University of Bristol
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Research output: Contribution to journal › Journal article – Annual report year: 2015 › Research › peer-review

The effect of maternal Inflammation on foetal programming of metabolic disease
Maternal obesity during pregnancy increases the child's risk of developing obesity and obesity-related diseases later in life. Key components in foetal programming of metabolic risk remain to be identified; however, chronic low-grade inflammation associated with obesity might be responsible for metabolic imprinting in the offspring. We have therefore surveyed the literature to evaluate the role of maternal obesity-induced inflammation in foetal programming of obesity and related diseases. The literature on this topic is limited, so this review also includes animal models where maternal inflammation is mimicked by single injections with lipopolysaccharide (LPS). An LPS challenge results in an immunological response that resembles the obesity-induced immune profile, although LPS injections provoke a stronger response than the subclinical obesity-associated response. Maternal LPS or cytokine exposures result in increased adiposity and impaired metabolic homeostasis in the offspring, similar to the phenotype observed after exposure to maternal obesity. The cytokine levels might be specifically important for the metabolic imprinting, as cytokines are both transferable from maternal to foetal circulation and have the capability to modulate placental nutrient transfer. However, the immune response associated with obesity is moderate and therefore potentially weakened by the pregnancy-driven immune modulation, dominated by anti-inflammatory Treg and Th2 cells. We know from other low-grade inflammatory diseases, such as rheumatoid arthritis, that pregnancy can improve disease state. If pregnancy is also capable of suppressing the obesity-associated inflammation, the immunological markers might be less likely to affect metabolic programming in the developing foetus than otherwise implied.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge

The effect of maternal Inflammation on foetal programming of metabolic disease
Maternal obesity during pregnancy increases the child's risk of developing obesity and obesity-related diseases later in life. Key components in foetal programming of metabolic risk remain to be identified; however, chronic low-grade inflammation associated with obesity might be responsible for metabolic imprinting in the offspring. We have therefore surveyed the literature to evaluate the role of maternal obesity-induced inflammation in foetal programming of obesity and related diseases. The literature on this topic is limited, so this review also includes animal models where maternal inflammation is mimicked by single injections with lipopolysaccharide (LPS). An LPS challenge results in an immunological response that resembles the obesity-induced immune profile, although LPS injections provoke a stronger response than the subclinical obesity-associated response. Maternal LPS or cytokine exposures result in increased adiposity and impaired metabolic homeostasis in the offspring, similar to the phenotype observed after exposure to maternal obesity. The cytokine levels might be specifically important for the metabolic imprinting, as cytokines are both transferable from maternal to foetal circulation and have the capability to modulate placental nutrient transfer. However, the immune response associated with obesity is moderate and therefore potentially weakened by the pregnancy-driven immune modulation, dominated by anti-inflammatory Treg and Th2 cells. We know from other low-grade inflammatory diseases, such as rheumatoid arthritis, that pregnancy can improve disease state. If pregnancy is also capable of suppressing the obesity-associated inflammation, the immunological markers might be less likely to affect metabolic programming in the developing foetus than otherwise implied.
An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity

Background
Multiple chemical sensitivity (MCS) is a medically unexplained condition characterized by reports of recurrent unspecific symptoms attributed to exposure to low levels of common volatile chemicals. The etiology of MCS is poorly understood, but dysregulation of the immune system has been proposed as part of the pathophysiology. Objective
To compare plasma levels of cytokines in Danish MCS individuals with a healthy, sex- and age-matched control group.

Method
Blood samples were obtained from 150 un-exposed MCS individuals and from 148 age- and sex-matched healthy controls. Plasma concentrations of 14 cytokines, chemokines and growth and allergen-specific IgE were measured. All participants completed a questionnaire including questions on MCS, psychological distress, morbidities and medication use at the time of the study. Results
Plasma levels of interleukin-1β, -2, -4, and -6 were significantly higher in MCS compared to controls.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Aleris-Hamlet Hospitals, Copenhagen University Hospital
Contributors: Dantoft, T. M., Elberling, J., Brix, S., Szecsi, P., Vesterhauge, S., Skovbjerg, S.
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Cesarean section imprints cord blood immune cell distributions

Immune programming in early life may affect the risk of developing immune-related diseases later in life. Children born by cesarean section seem to be at higher risk of asthma, allergic rhinitis, and type-1 diabetes. We hypothesized that delivery
by cesarean section may affect immune maturation in newborns. The objective of the study was to profile innate and adaptive immune cell subsets in cord blood of children born by cesarean section or natural birth.

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- **Organisations:** Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen
- **Contributors:** Thysen, A. H., Larsen, J. M., Rasmussen, M. A., Stokholm, J., Bønnelykke, K., Pedersen, S. B., Bisgaard, H. F.
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**Children developing asthma by school-age display aberrant immune responses to pathogenic airway bacteria as infants**

Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonisation of neonatal airways with the pathogenic bacterial strains H. influenzae, M. catarrhalis and S. pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children developing asthma have an abnormal immune response to pathogenic bacteria in infancy. We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years.

**General information**
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- **Organisations:** Department of Systems Biology, Center for Biological Sequence Analysis, Department of Biochemistry and Nutrition, Copenhagen University Hospital, University of Copenhagen
- **Contributors:** Larsen, J. M., Pedersen, S. B., Thysen, A. H., Birch, S., Rasmussen, M., Bisgaard, H.
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- **Original language:** English
- **Source:** FindIt
- **Source-ID:** 271169311
Children with asthma by school age display aberrant immune responses to pathogenic airway bacteria as infants

Background: Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonization of neonatal airways with the pathogenic bacterial strains Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children with asthma have an abnormal immune response to pathogenic bacteria in infancy. Objective: We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years. Methods: The Copenhagen Prospective Studies on Asthma in Childhood birth cohort was followed prospectively, and asthma was diagnosed at age 7 years. The immune response to H. influenzae, M. catarrhalis, and S. pneumoniae was analyzed in 292 infants using PBMCs isolated and stored since the age of 6 months. The immune response was assessed based on the pattern of cytokines produced and T-cell activation. Results: The immune response to pathogenic bacteria was different in infants with asthma by 7 years of age (P = .0007). In particular, prospective asthmatic subjects had aberrant production of IL-5 (P = .008), IL-13 (P = .057), IL-17 (P = .001), and IL-10 (P = .028), whereas there were no differences in T-cell activation or peripheral T-cell composition. Conclusions: Children with asthma by school age exhibited an aberrant immune response to pathogenic bacteria in infancy. We propose that an abnormal immune response to pathogenic bacteria colonizing the airways in early life might lead to chronic airway inflammation and childhood asthma.

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Keywords: COPSAC - Copenhagen Prospective Studies on Asthma in Childhood, FACS - Fluorescence-activated cell sorting, NK - Natural killer, PC - Principal component, PCA - Principal component analysis, TCR - T-cell receptor
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Early immune response patterns to pathogenic bacteria are associated to increased risk of lower respiratory infections in children

Neonatal colonisation of the airways with respiratory pathogens is associated with increased risk of lower respiratory infections (LRI) in early childhood (1). Therefore, we hypothesized that children developing LRI have an abnormal immune response to pathogenic bacteria in infancy. We aimed to characterise the systemic immune response to pathogenic bacteria at the age of 6 months and study the association with incidence of LRI during the first 3 years of life.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen
Contributors: Vissing, N. H., Larsen, J. M., Rasmussen, M. A., Thyssen, A. H., Chawes, B. L., Bønnelykke, K., Pedersen, S. B., Bisgaard, H. F.
Number of pages: 1
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Publication date: 2014
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Effects of pregnancy on obesity-induced inflammation in a mouse model of fetal programming

Objective
Maternal obesity is associated with increased risk of metabolic dysfunction in the offspring. It is not clear whether it is the metabolic changes or chronic low-grade inflammation in the obese state that causes this metabolic programming. We therefore investigated whether low-grade inflammation was present in obese dams compared to controls dams at gestation day 18.

Methods
Female mice were fed either a standard chow diet or a highly palatable obesogenic diet for 6 weeks prior to conception. Mice were either euthanized before mating (n=12 in each group), or euthanized on gestation day 18 (n=8 in each group). Blood and tissues were collected for analysis.

Results
The obesogenic diet increased body weight and decreased insulin sensitivity prior to conception, while there was no difference between the groups at gestation day 18. Local inflammation was assayed by macrophage count in adipose tissue and liver. Macrophage count in the adipose tissue was increased significantly by the obesogenic diet, and the hepatic count also showed a tendency to increased macrophage infiltration prior to gestation. This was further supported by a decreased population of monocytes in the blood of the obese animals, which suggested that monocytes are being recruited from the blood to the liver and adipose tissue in the obese animals. Gestation reversed macrophage infiltration, such that obese dams showed a lower adipose tissue macrophage count at the end of gestation compared to pre-pregnancy obese mice, and there were no longer a tendency towards increased hepatic macrophage count. Placental macrophage count was also similar in the two groups.

Conclusion
At gestation day 18, obese dams were found to have similar macrophage infiltration in placenta, adipose tissue and liver as lean dams, despite an incipient infiltration before gestation. Thus, the obesity-induced inflammation was reversed during gestation.
Gliadin affects glucose homeostasis and intestinal metagenome in C57BL/6 mice fed a high-fat diet

Dietary gluten and its component gliadin are well-known environmental triggers of celiac disease and important actors in type-1 diabetes, and are reported to induce alterations in the intestinal microbiota. However, research on the impact of gluten on type-2 diabetes in non-celiac subjects is more limited. The aim of this study was to investigate the effect of gliadin on glucose homeostasis and intestinal ecology in the mouse. Forty male C57BL/6 mice were fed a high-fat diet containing either 4% gliadin or no gliadin for 22 weeks. Gliadin consumption significantly increased the HbA1c level over time, with a borderline significance of higher HOMA-IR (homeostasis model assessment of insulin resistance) after 22 weeks. Sequencing of the V3 region of the bacterial 16S rRNA genes showed that gliadin changed the abundance of 81 bacterial taxa, separating the intestinal microbial profile of the gliadin consuming mice from the control mice in the principal coordinate analysis (PCoA) of weighted UniFrac distance. No difference was found in body weight gain, feed consumption or circulating cytokines (IL-1β, IL-6, IFN-γ, TNF-α and IL-10). Our study is the first to show that gliadin as part of a defined synthetic feed exacerbates the glycaemia and alters the intestinal microbiota composition. Comprehensive analyses of the profile of specific immune cells, metabolites and intestinal permeability are in progress to elucidate the mechanism behind the observed effects.

Interaction of Lactobacillus acidophilus NCFM grown on different carbohydrates with human intestinal epithelial cells: Adhesion Properties and roles of S-layer Proteins

Mycobacterium tuberculosis promotes Th17 expansion via regulation of human dendritic cells toward a high CD14 and low IL-12p70 phenotype that reprograms upon exogenous IFN-γ.

The capacity to develop protective immunity against mycobacteria is heterogeneously distributed among human beings, and it is currently unknown why the initial immune response induced against Mycobacterium tuberculosis (Mtb) does not
provide proper clearance of this pathogen. Dendritic cells (DCs) are some of the first cells to interact with Mtb and they play an essential role in development of protective immunity against Mtb. Given that Mtb-infected macrophages have difficulties in degrading Mtb, they need help from IFN-γ-producing CD4+ T cells propagated via IL-12p70-producing DCs. Here we report that Mtb modifies human DC plasticity by expanding a CD14+ DC subset with weak IL-12p70-producing capacity. The CD14+ Mtb-promoted subset was furthermore poor inducers of IFN-γ by naive CD4+ T cells, but instead prompted IL-17A-producing RORγT+ CD4+ T cells. Mtb-derived peptidoglycan and mannosylated lipoarabinomannan partly recapitulated the subset partition induced by Mtb. Addition of IFN-γ, but neither IL-17A nor IL-22, which are potentially produced by Mtb-exposed γ/δ-T cells in mucosal linings, inhibited the differentiation toward CD14+ DCs and promoted high-level IL-12p70 in Mtb-challenged DCs. We conclude that Mtb exploits DC plasticity to reduce production of IL-12p70, and that this process is entirely divertible by exogenous IFN-γ. These data suggest that strategies to increase local IFN-γ production in the lungs of tuberculosis patients may boost host immunity toward Mtb.

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Contributors: Søndergaard, J. N., Laursen, J. M., Rosholm, L. B., Pedersen, S. B.
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Natural mannosylation of HIV-1 gp120 imposes no immunoregulatory effects in primary human plasmacytoid dendritic cells
Plasmacytoid dendritic cells (pDCs) play a vital role in activation of anti-HIV-1 immunity, and suppression of pDCs might mitigate immune responses against HIV-1. HIV-1 gp120 high-mannose has been attributed immunosuppressive roles in human myeloid DCs, but no receptors for high-mannose have so far been reported on human pDCs. Here we show that upon activation with HIV-1 or by a synthetic compound triggering the same receptor in human pDCs as single-stranded RNA, human pDCs upregulate the mannose receptor (MR, CD206). To examine the functional outcome of this upregulation, inactivated intact or viable HIV-1 particles with various degrees of mannosylation were cultured with pDCs. Activation of pDCs was determined by assaying secretion of IFN-alpha, viability, and upregulation of several pDC-activation markers: CD40, CD86, HLA-DR, CCR7, and PD-L1. The level of activation negatively correlated with degree of mannosylation, however, subsequent reduction in the original mannosylation level had no effect on the pDC phenotype. Furthermore, two of the infectious HIV-1 strains induced profound necrosis in pDCs, also in a mannose-independent manner. We therefore conclude that natural mannosylation of HIV-1 is not involved in HIV-1-mediated immune suppression of pDCs.

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Statens Serum Institut
Contributors: Søndergaard, J. N., Vinner, L., Pedersen, S. B.
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Journal: Molecular Immunology
Deep phenotyping of the unselected COPSAC2010 birth cohort study

We hypothesize that perinatal exposures, in particular the human microbiome and maternal nutrition during pregnancy, interact with the genetic predisposition to cause an abnormal immune modulation in early life towards a trajectory to chronic inflammatory diseases such as asthma and others. The aim of this study is to explore these interactions by conducting a longitudinal study in an unselected cohort of pregnant women and their offspring with emphasis on deep clinical phenotyping, exposure assessment, and biobanking. Exposure assessments focus on the human microbiome. Nutritional intervention during pregnancy in randomized controlled trials are included in the study to prevent disease and to be able to establish causal relationships. Pregnant women from eastern Denmark were invited during 2008–2010 to a novel unselected ‘COPSAC2010’ cohort. The women visited the clinic during pregnancy weeks 24 and 36. Their children were followed at the clinic with deep phenotyping and collection of biological samples at nine regular visits until the age of 3 and at acute symptoms. Randomized controlled trials of high-dose vitamin D and fish oil supplements were conducted during pregnancy, and a trial of azithromycin for acute lung symptoms was conducted in the children with recurrent wheeze. Seven hundred and thirty-eight mothers were recruited from week 24 of gestation, and 700 of their children were included in the birth cohort. The cohort has an over-representation of atopic parents. The participant satisfaction was high and the adherence equally high with 685 children (98%) attending the 1 year clinic visit and 667 children (95%) attending the 2 year clinic visit. The COPSAC2010 birth cohort study provides longitudinal clinical follow-up with highly specific endpoints, exposure assessments, and biobanking. The cohort has a high adherence rate promising strong data to elucidate the interaction between genomics and the exposome in perinatal life leading to lifestyle-related chronic inflammatory disorders such as asthma.

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Effect of gestation on obesity-induced hepatic and placental inflammation in mice

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Epithelial entry rather than the ensuing systemic immune response determines the pathogenicity of two Salmonella enterica serovar Typhimurium strains in a mouse model

Most studies of Salmonella enterica serovar Typhimurium infection focus only on the pathogenicity of one strain. We investigated whether differences in pathogenicity of two wild-type S. Typhimurium strains, DT120 and SL1344, were related to gut invasion or the resulting immune response. Oral administration of a ten-fold lower number of SL1344 (106 CFU) as compared to DT120 (107 CFU) resulted in higher bacterial counts in liver and lymph nodes, and led to massive neutrophil infiltration of the spleen, while DT120 administration did not. In contrast, administration of the same dose (103 CFU) of the two strains intravenously resulted in the same levels of bacteria and neutrophils in spleen and bone marrow. Oral administration of SL1344 led to an increase in neutrophil apoptosis in both spleen and the bone marrow and four out of five mice died before Day 8, while in DT120 mice, no increase in neutrophil apoptosis was observed and all mice survived until Day 8. This study reveals that two wild-type S. Typhimurium strains, despite evoking highly comparable immune responses upon intravenous injection, exhibit diverse pathogenicity in mice and thus suggests that differences in their invasiveness and survival during gut passage determines the success of the ensuing immune response.
Functional Similarities and Disparities in Inflammation-Promoting Abilities of Gut-Derived Escherichia coli Strains from Patients with Inflammatory Bowel Diseases and Healthy Individuals

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Statens Serum Institut, Technical University of Denmark, University Hospital Herlev, University of Copenhagen
Contributors: Jensen, S. R., Mirsepasi, H., Thysen, A., Brynskov, J., Krogfelt, K., Petersen, A. M., Pedersen, A. E., Pedersen, S. B.
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ISI indexed (2013): ISI indexed yes
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Original language: English
Source: dtu
Source-ID: u::10264
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2013 › Research › peer-review

Gestation reverses obesity-induced hepatic inflammation in mice

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Gestation reverses obesity-induced hepatic inflammation in mice

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Publication status: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge
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Publication information
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Volume: 92
Gut Mucosal Regulation of Distinct Macrophage and Dendritic Cell Subsets During Early Stage Salmonella Infection

General information
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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, National Food Institute, Division of Food Microbiology
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High-Mannose Glycosylation of Infectious HIV-1 gp120 and Immune Regulation in Human Plasmacytoid Dendritic Cells

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Contributors: Søndergaard, J. N., Vinner, L., Pedersen, S. B.
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Web of Science (2013): Impact factor 1.882
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

The causative agent of tuberculosis, Mycobacterium tuberculosis, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most M. tuberculosis infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium. The dendritic cell (DC) plays a crucial role in shaping the nature of the immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.

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Organisations: Department of Systems Biology, Cellular Signal Integration
Contributors: Laursen, J. M., Schoof, E., Søndergaard, J. N., Linding, R., Pedersen, S. B.
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Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

The causative agent of tuberculosis, Mycobacterium tuberculosis, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most M. tuberculosis infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium. The dendritic cell (DC) plays a crucial role in shaping the nature of the immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.

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Organisations: Department of Systems Biology, Cellular Signal Integration
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Identification of a novel immunoregulatory signaling pathway exploited by M. tuberculosis in dendritic cells

The causative agent of tuberculosis, Mycobacterium tuberculosis, has infected over a third of the world's population and poses a massive burden to health care systems and human well-being. Most M. tuberculosis infections are latent and are not cleared fully by the host immune system due to the highly sophisticated infectious machinery employed by the bacterium. The dendritic cell (DC) plays a crucial role in shaping the nature of the immune response after exposure to pathogens, and the interaction between M. tuberculosis and the dendritic cell is of profound importance for the course of infection. During their interaction, the DC is exposed to multiple M. tuberculosis-derived ligands recognized by a range of pattern recognition receptors, but the result is typically an immune response that is not very effective at clearing the bacteria from the host. The reason why the induced immune response is ineffective at clearing the bacteria is not fully understood, but clues may be given in the signaling pathways induced in DCs upon M. tuberculosis-exposure.
Molecular signaling networks in regulation of immunity and disease

The gut microbiota, host tissues, and the immune system form a complex network where extensive crosstalk and molecular interactions substantially impact the overall state of the system. Concomitantly, modulation of host immune function is recurrently a result of the interaction of complex and dynamic microbial communities with the immune cell compartment in the gut, and therefore the interaction between components from different gut bacteria can efficiently shape the phenotype of the immune response.
A specialized antigen-presenting cell present at mucosal surfaces, the dendritic cell (DC), plays a crucial role in shaping the nature of the adaptive/memory-based immune response after encountering inflammatory compounds. In the gut, the DC is continuously exposed to microbial and dietary components that are recognized by its innate pattern recognition receptors, and the phenotype developed in the DC during activation is of profound importance for the state of immune response and thereby also affects the inflammatory and metabolic status in tissues.

We have shown that specific fermentation products from gut bacteria have distinct immunoregulatory effects that effectively inhibit the proinflammatory properties of common gut commensals. We are currently looking into the mechanisms behind the antiinflammatory effects of the microbial fermentation products with a specific interest in the complex interactions between enzymes catalyzing posttranslational modifications, transcription factors and other molecules that make up the intracellular signaling networks in DCs and shape specific DC phenotypes of importance for health and disease.

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Contributors: Laursen, J. M., Jensen, S. R., Sørensen, M., Pedersen, S. B.
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**Obesity-induced hepatic and placental inflammation are absent in obese gestating mice compared to control fed dams**

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Cambridge
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**Pathogenic bacteria colonizing the airways in asymptomatic neonates stimulates topical inflammatory mediator release.**

Rationale: Bacterial colonization of neonatal airways with the pathogenic bacterial species, Moraxella catarrhalis, Streptococcus pneumoniae, and Haemophilus influenzae, is associated with later development of childhood asthma.

Objectives: To study a possible association between colonization with pathogenic bacterial strains and the immune signature of the upper airways in healthy neonates.

Methods: A total of 20 cytokines and chemokines were quantified in vivo in the airway mucosal lining fluid of 662 neonates from the Copenhagen Prospective Study of Asthma in Childhood 2010 birth cohort. Colonization of the hypopharynx with M. catarrhalis, S. pneumoniae, H. influenzae, and Staphylococcus aureus was assessed simultaneously. The association between immune signatures and bacterial colonization or noncolonized controls was analyzed using conventional statistical methods supplemented by a multivariate approach for pattern identification.

Measurements and Main Results: Colonization with M. catarrhalis and H. influenzae induced a mixed T helper cell (Th) type 1/Th2/Th17 response with high levels of IL-1 beta (M. catarrhalis, P = 2.2 x 10(-12); H. influenzae, P = 7.1 X 10(-10)), TNF-alpha (M. catarrhalis, P = 1.5 x 10(-9); H. influenzae, P = 5.9 x 10(-7)), and macrophage inflammatory protein-1 beta (M. catarrhalis, P = 1.6 X 10(-11); H. influenzae, P = 2.7 x 10(-7)). S. aureus colonization demonstrated a Th17-promoting profile with elevated IL-17 levels (P = 1.6 x 10(-24)). S. pneumoniae colonization was not significantly associated with any of the mediators.

Conclusions: M. catarrhalis and H. influenzae colonization of the airways of asymptomatic neonates is associated with an
inflammatory immune response of the airway mucosa, which may result in chronic inflammation.

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Contributors: Følsgaard, N. V., Schjørring, S., Chawes, B. L. K., Rasmussen, M., Krogfelt, K. A., Pedersen, S. B., Bisgaard, H. F.
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**Perinatal Environmental Effects on the Neonatal Immune System**

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Contributors: Thysen, A. H., Pedersen, S. B., Bisgaard, H.
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Supervisors Susanne Brix Pedersen and Hans Bisgaard (Cph Uni).
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**Perinatal programming of metabolic dysfunction and obesity-induced inflammation**
The number of obese women in the childbearing age is drastically increasing globally. As a consequence, more children are born by obese mothers. Unfortunately, maternal obesity and/or high fat intake during pregnancy increase the risk of developing obesity, type-2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease in the children, which passes obesity and metabolic dysfunction on from generation to generation. Several studies try to elucidate causative effects of maternal metabolic markers on the metabolic imprinting in the children; however diet induced obesity is also associated with chronic low grade inflammation. Nobody have yet investigated the role of this inflammatory phenotype, but here we demonstrate that obesity induced inflammation is reversed during pregnancy in mice, and is therefore less likely to affect the fetal programming of metabolic dysfunction. Instead, we suggest that an early elevated lipid exposure caused by a maternal high fat feeding might be more important for long term metabolic imprinting in the offspring. Therefore, we study the effect of maternal high fat/high sucrose diet during gestation, lactation or both to elucidate if perinatal adaptations to a high fat/high sucrose diet makes the offspring more capable of dealing with a high fat diet later in life. We
demonstrate that a dietary mismatch between pre- and post-natal life alters the phenotype in an obese prone rat model at weaning. Thus, exposure to a control diet in utero and a high fat/high sucrose diet during lactation cause more severe phenotypic alteration in the offspring at weaning than pups exposed to the high fat/high sucrose diet both in utero and during lactation. The same pattern is seen in the adult offspring after being challenged with a high fat diet for 6 weeks. However HFHS exposure during fetal life protected against hyperleptinemia in the adult offspring during the challenge. Additionally, offspring exposed to high fat/high sucrose diet during lactation displayed a decrease level of inflammatory genes in the blood, which could indicated that perinatal HFHS exposure protect against the detrimental effects of high fat feeding leading to metabolic disease.

Divergent pro-inflammatory profile of human dendritic cells in response to commensal and pathogenic bacteria associated with the airway microbiota.

Recent studies using culture-independent methods have characterized the human airway microbiota and report microbial communities distinct from other body sites. Changes in these airway bacterial communities appear to be associated with inflammatory lung disease, yet the pro-inflammatory properties of individual bacterial species are unknown. In this study, we compared the immune stimulatory capacity on human monocyte-derived dendritic cells (DCs) of selected airway commensal and pathogenic bacteria predominantly associated with lungs of asthma or COPD patients (pathogenic Haemophilus spp. and Moraxella spp.), healthy lungs (commensal Prevotella spp.) or both (commensal Veillonella spp. and Actinomyces spp.). All bacteria were found to induce activation of DCs as demonstrated by similar induction of CD83, CD40 and CD86 surface expression. However, asthma and COPD-associated pathogenic bacteria provoked a 3-5 fold higher production of IL-23, IL-12p70 and IL-10 cytokines compared to the commensal bacteria. Based on the differential cytokine production profiles, the studied airway bacteria could be segregated into three groups (Haemophilus spp. and Moraxella spp. vs. Prevotella spp. and Veillonella spp. vs. Actinomyces spp.) reflecting their pro-inflammatory effects on DCs. Co-culture experiments found that Prevotella spp. were able to reduce Haemophilus influenzae-induced IL-12p70 in DCs, whereas no effect was observed on IL-23 and IL-10 production. This study demonstrates intrinsic differences in DC stimulating properties of bacteria associated with the airway microbiota.
Isolation of IL-12p70-competent human monocyte-derived dendritic cells

Diverse methodologies ranging from experimental immunological studies to immunotherapy involve the application of human monocyte-derived dendritic cells (moDCs). Considerable donor-dependent variations in the moDC production of IL-12p70 affect the outcome of these methodologies. It has been shown that moDCs generated under standard conditions develop into two subsets based on CD1a-expression with the CD1a+ moDCs being the main IL-12p70 producers. This has however not been generally accepted, which we show here because the subset described as CD1a-negative does express CD1a, but at a lower level than the other subset. We further characterize the phenotype of these two subsets, showing that the CD1a-hi subset has a greater immunogenic phenotype, making this subset more suitable for immunotherapy. The two subsets have previously been separated by cell sorting, but as this technique is not available to many laboratories and has incompatibility with clinical settings, a more widely useable technique is warranted. Therefore we tested if magnetic-activated cell sorting is useful for the purpose, and show that it is possible to isolate IL-12p70-competent CD1a-hi moDCs to a...
Neonatal Cytokine Profile in the Airway Mucosal Lining Fluid Is Skewed by Maternal Atopy

Rationale: Heredity from mother or father may impact differently in complex diseases, such as atopy. Maternal atopy is a stronger risk factor than paternal atopy for the development of atopy in the offspring. We hypothesized that mother’s and father’s atopy would have a differential imprinting on the cytokines and chemokines in the upper airway mucosal lining fluid of healthy neonates. Objectives: To study parental atopic imprinting on the cytokines and chemokines in the upper airway mucosal lining fluid of healthy neonates. Methods: Eighteen cytokines and chemokines were quantified in nasal mucosal lining fluid in 309 neonates from the novel unselected Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort. Measurements and Main Results: Maternal, but not paternal, atopic status (asthma, hay fever, or eczema with or without sensitization) was associated with general down-regulation of all 18 mediators assessed by principal component analysis (overall P = 0.015). Conclusions: Maternal atopy, but not paternal atopy, showed a strong linkage with a suppressed mucosal cytokine and chemokine signature in asymptomatic neonates, suggesting imprinting by the maternal milieu in utero or perinatal life.

Upregulation of TGF-beta 1 in neonates of mothers receiving Influenza A (H1N1) vaccination during pregnancy

Background: Influenza vaccination of pregnant women is generally considered safe, but the effects on the immune system of the unborn child are unknown. Objectives: Our primary objective was to explore differences in cytokine and chemokine levels in nasal mucosal lining fluid in neonates of mothers vaccinated during or after pregnancy. Method: IFN-c, IL-1b, IL-2, -4, -5, -10, -12p70, -13, -17, TNF-a, IL-8, eotaxin-1, eotaxin-3, IP-10, MCP-1, MCP-4, MDC, MIP-1b, TGF-b1 and TARC were quantified in nasal mucosal lining fluid in neonates of mothers receiving Influenza A (H1N1v) vaccine during (n = 52) or after pregnancy (n = 118) in our unselected Copenhagen Prospective Study on Asthma in Childhood 2010 birth-cohort. Result: Neonates of mothers vaccinated during pregnancy showed a significant up-regulation of the immune-regulatory TGF-b1 (P = 0.0004), significant down regulation (P < 0.05) of TARC, IL-5, IL-8, IL-10, IFN-c, IL-12, MCP-1, MCP-4, MDC, MIP-1b, TGF-b1 and TARC were quantified in nasal mucosal lining fluid in neonates of mothers receiving Influenza A (H1N1v) vaccine during (n = 52) or after pregnancy (n = 118) in our unselected Copenhagen Prospective Study on Asthma in Childhood 2010 birth-cohort. Result: Neonates of mothers vaccinated during pregnancy showed a significant up-regulation of the immune-regulatory TGF-b1 (P = 0.0004), significant down regulation (P < 0.05) of TARC, IL-5, IL-8, IL-10, IL-12p70, eotaxin-1, MDC, IFN-c and non-significant down regulation of nearly all other mediators except for MCP-4, IL-17, eotaxin-3 compared to neonates of mothers vaccinated after pregnancy. Results are adjusted for season; airway colonization S. pneumoniae, H. influenzae, M. catarrhalis, and S. aureus; older siblings; furred animals in home; smoking during 3rd trimester; and mothers’ atopic disease. Conclusion: These findings suggest that Influenza A (H1N1) vaccination during pregnancy affects the mucosal
immune competence of the unborn child. The up-regulation of TGF-b1 and down-regulation of nearly all essential contributors to protective immunity reflect an imprinting suggestive of immune inhibition that may affect the neonates' ability to combat respiratory tract infections.

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**Are NOD2 polymorphisms linked to a specific disease endophenotype of Crohn’s disease?**
The complex and yet unknown etiology of Crohn’s disease (CD) might consist of various disease endophenotypes, each of which represent their own pathogenesis. This review focuses on the disease endophenotype linked to polymorphisms in the nucleotide-binding oligomerization domain containing 2 (NOD2) protein and on the importance of established adherent-invasive E. coli (AIEC) in ileal mucosa. To date, there are several reports pointing to the implications of NOD2 polymorphisms in epithelial and immunological responses against microbes, but the pathological significance of NOD2 mutations in CD is not yet clarified. The enhanced number of pathogenic E. coli in the ileal mucosa of CD as compared to healthy controls may result from a genetically based failure in one of the intestinal bacteria sensing systems, like NOD2, making the ileal epithelium more prone to colonization with microbes harboring specific properties such as AIEC. Increasing the focus on defining subgroups of patients with similar disease initiations, mechanisms of action, and manifestations in CD may be pivotal for the development and implementation of future individualized treatment strategies of benefit for the single patient at an early stage. (Inflamm Bowel Dis 2011;)

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Comparative analysis of a large panel of non-starch polysaccharides reveals structures with selective regulatory properties in dendritic cells

Scope: Structural-based recognition of foreign molecules is essential for activation of dendritic cells (DCs) that play a key role in regulation of gut mucosal immunity. Orally ingested non-starch polysaccharides (NSP) are ascribed many health-promoting properties, but currently we lack insight into the impact of structure and size for their capacity to affect immune responses. Methods and results: This study addresses the importance of chemical structure, size, origin and presence of contaminants for the capacity of both dietary and non-food NSP to modulate DC. Of 28 NSP products, β-glucans of microbial and plant origin and the galactomannan guar gum were found to modulate the DC cytokine pattern induced by the Toll-like receptor 4-ligand LPS giving rise to reduced IL-12p70 and increased IL-10 levels, whereas IL-6 production was unaffected. A large proportion of the tested NSP were able to down-regulate LPS-induced IL-12p70 production. The most potent NSP induced up-regulation of CD86 on DC independently of LPS stimulation. Cereal-based β-glucans showed less potency than β-glucans of microbial origin, but proper molecular weight composition and preparation may improve effectiveness. Conclusions: Collectively, this comparative study revealed that some plant-derived NSP besides those of microbial origin exert modulation of the DC phenotype, with the exact structure being important for the activity.

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Diversion of flux toward sesquiterpene production in Saccharomyces cerevisiae by fusion of host and heterologous enzymes.

The ability to transfer metabolic pathways from the natural producer organisms to the well-characterized cell factory Saccharomyces cerevisiae is well documented. However, as many secondary metabolites are produced by collaborating enzymes assembled in complexes, metabolite production in yeast may be limited by the inability of the heterologous enzymes to collaborate with the native yeast enzymes. This may cause loss of intermediates by diffusion or degradation or due to conversion of the intermediate through competitive pathways. To bypass this problem, we have pursued a strategy in which key enzymes in the pathway are expressed as a physical fusion. As a model system, we have constructed
several fusion protein variants in which farnesyl diphosphate synthase (FPPS) of yeast has been coupled to patchoulol synthase (PTS) of plant origin (Pogostemon cablin). Expression of the fusion proteins in S. cerevisiae increased the production of patchoulol, the main sesquiterpene produced by PTS, up to 2-fold. Moreover, we have demonstrated that the fusion strategy can be used in combination with traditional metabolic engineering to further increase the production of patchoulol. This simple test case of synthetic biology demonstrates that engineering the spatial organization of metabolic enzymes around a branch point has great potential for diverting flux toward a desired product. ©American Society for Microbiology. All rights reserved.

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**Ex vivo intestinal adhesion of Escherichia coli LF82 in Crohn's disease**
Adherent-invasive Escherichia coli (AIEC) are reported to inhabit the gut mucosa in Crohn’s disease (CD), however, little is known about the importance of host factors for the interplay between AIEC and the human gut. To examine if differences in bacterial adhesion patterns are disease associated, the AIEC-prototype strain LF82 was evaluated for its ability to adhere to ileal and colonic biopsies from CD and healthy controls (HC). Moreover, the efficacy of the non-pathogenic E. coli Nissle 1917 (ECN) in averting LF82 adhesion to ileal mucosa was assessed. Similar numbers of LF82 adhered to biopsies from CD and HC. A significantly greater LF82 attachment to ileal versus colonic mucosa was found in HC (P <0.01), however, not in CD. ECN did not reduce the adhesion of LF82 to ileal specimens in CD or HC. These results show that enhanced bacterial adhesion ability is unlikely to play any significant role in CD, thus implying that other host protective factors may be impaired in CD. Further, exclusion of LF82 attachment by ECN co-incubation does not appear to represent a relevant treatment regimen.

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Ileal adhesion of virulent E. coli LF82 is not enhanced in Crohn's disease.

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IIleal adhesion of virulent E. coli LF82 is not enhanced in Crohn’s disease

Adherent-invasive Escherichia coli (AIEC) comprise a new group of E. coli species named from their distinctive ability to adhere to and invade the intestinal epithelium. The AIEC strains have been associated to the ileal mucosa in Crohn’s disease (CD), and the impact of AIEC in the pathogenesis of CD has been further strengthened from the evidence that the ileum in CD harbors an abnormally high number of E. coli species. S16 2010 IBD Abstracts The aim of this study was to examine the adhesion of the AIEC reference strain, LF82, to tissue samples from ileum and colon in CD and healthy controls. A second purpose was to assess the probiotic efficacy of E. coli Nissle 1917 (ECN) in averting LF82 adhesion to ileal mucosa. Ileal and colonic specimens were obtained from patients with CD ileitis and controls (n=10). A model was developed to investigate bacterial adhesion to intestinal biopsies and comprised: 1) incubation of tissue (inclusive of mucous) with 10^7 bacteria or buffer for 1 hour, 2) removal of non-adhered bacteria by extensive washing, and 3) absolute quantification of tissue-adhered LF82 and indigenous E. coli by a pre-validated assay including quantitative real-time PCR. Selective primers- and probes were designed specifically for targeting the pMT1-like plasmid in LF82 and E. coli 16S ribosomal DNA for quantifying the general E. coli population. Bacterial numbers were related to tissue weight. A thoroughly validated model with a coefficient of variation <2 % was developed and employed for investigation of the bacterial adherence to human intestinal specimens. LF82 adhered to intestinal biopsies in both CD and healthy controls. A second purpose was to assess the probiotic efficacy of E. coli Nissle 1917 (ECN) in averting LF82 adhesion to ileal mucosa. Ileal and colonic specimens were obtained from patients with CD ileitis and controls (n=10). A model was developed to investigate bacterial adhesion to intestinal biopsies and comprised: 1) incubation of tissue (inclusive of mucous) with 107 bacteria or buffer for 1 hour, 2) removal of non-adhered bacteria by extensive washing, and 3) absolute quantification of tissue-adhered LF82 and indigenous E. coli by a pre-validated assay including quantitative real-time PCR. Selective primers- and probes were designed specifically for targeting the pMT1-like plasmid in LF82 and E. coli 16S ribosomal DNA for quantifying the general E. coli population. Bacterial numbers were related to tissue weight. A thoroughly validated model with a coefficient of variation <2 % was developed and employed for investigation of the bacterial adherence to human intestinal specimens. LF82 adhered to intestinal biopsies in both CD and healthy controls. Enhanced adhesion was, however, not observed in the ileum as compared to the colon in CD, which was in contradiction to controls that had a significantly higher LF82-attachment to the ileal epithelium as compared to that of the colon (P <0.01). The variation in LF82 adhesion between ileal and colonic specimens was more prominent in CD than in controls. Although not statistically significant, a trend towards higher counts of indigenous E. coli was observed in the ileum as compared to the colon of CD, and the number of indigenous LF82 and total E. coli bacteria tended to be inversely correlated in both ileum and colon tissue. Further, ECN did not avert the adhesion of LF82 to ileal specimens, but instead ECN likely favoured LF82 adhesion particularly in CD. ECN did also adhere to the ileal mucosa. Conclusively it was shown that LF82 preferentially adhere to ileal tissue in controls, but not in CD suggesting that the intestinal microenvironment of the colon is changed in terminal ileitis. Co-incubation with ECN tended to increase ileal LF82 adhesion, thus highlighting that careful mechanistic studies are warranted before including ECN in clinical studies. The current study demonstrates a
great variability in host LF82 interactions within the group of patients with CD ileitis, thus stressing individual response patterns against LF82.

Probiotika

Quantification of specific E. coli in gut mucosa from Crohn's disease patients

We here present a method based on qRT-PCR to quantify E. coli LF82 in intestinal human samples. Two different primer-probe sets were designed to detect LF82, and a third to target total E. coli. The assay showed high robustness and specificity for detection of LF82 in the presence of intestinal tissue.
The pathogenicity of S. Typhimurium SL1344 is coupled to invasiveness and not the ensuing immune response

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Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Division of Microbiology and Risk Assessment, National Food Institute
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CD4+ T-cell activation is differentially modulated by bacteria-primed dendritic cells, but is generally down-regulated by n-3 polyunsaturated fatty acids

Appropriate activation of CD4+ T cells is fundamental for efficient initiation and progression of acquired immune responses. Here, we showed that CD4+ T-cell activation is dependent on changes in membrane n-3 polyunsaturated fatty acids (PUFAs) and is dynamically regulated by the type of signals provided by dendritic cells (DCs). Upon interaction with DCs primed by different concentrations and species of gut bacteria, CD4+ T cells were activated according to the type of DC stimulus. The levels of CD80 were found to correlate to the levels of expression of CD28 and to the proliferation of CD4+ T cells, while the presence of CD40 and CD86 on DCs inversely affected inducible costimulator (ICOS) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) levels in CD4+ T cells. For all DC stimuli, cells high in n-3 PUFAs showed reduced ability to respond to CD28 stimulation, to proliferate, and to express ICOS and CTLA-4. Diminished T-cell receptor (TCR) and CD28 signalling was found to be responsible for n-3 PUFA effects. Thus, the dietary fatty acid composition influences the overall level of CD4+ T-cell activation induced by DCs, while the priming effect of the DC stimuli modulates CD80, CD86 and CD40 levels, thereby affecting and shaping activation of acquired immunity by differential regulation of proliferation and costimulatory molecule expression in CD4+ T cells.

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Publication information
Dietary fibers as immunoregulatory compounds in health and disease

Many nonstarch polysaccharides (NSPs) classified as dietary fibers have been reported to possess immunoregulatory properties. The fibers reported to activate or by other means modulate immune responses originate from both plant, fungal, and microbial sources and constitute highly distinct structures. In order to enhance our understanding of factors important for the immunoregulatory activities, this article addresses the importance of chemical structure, origin, and purity of fibers for their capacity to interact with key regulatory immune cells. Furthermore, we assess bioavailability, and discuss possible mechanisms involved. The binding of some NSPs to carbohydrate receptors on immune cells is well established and this event leads to activation or other changes. Especially, certain beta-glucans and some mannans have demonstrated immunomodulatory capacity with the specific structure being important for the activity. Within beta-glucans the activity varies according to structure, molecular weight, and solubility. As many of the preparations tested constitute crude extracts or partly purified NSPs, the risk of contaminants holding immunoregulatory activities should not be ignored. To what extent NSPs enter systemic circulation has been difficult to assess, partly due to lack of sensitive analytical methods. The presence of NSPs in blood and Peyer's patches in the gut has been demonstrated, supporting encounter between NSPs and immune cells, but bioavailability studies still constitute a major challenge. Studies demonstrating in vivo effects of beta-glucans on microbial infections and cancer treatment strongly indicate an immunoregulatory mechanism behind the effects. However, the potential of NSPs as immunoregulatory food ingredients is still far from fully explored.

Pseudomonas aeruginosa quorum-sensing signal molecules interfere with dendritic cell-induced T-cell proliferation

Pseudomonas aeruginosa releases a wide array of toxins and tissue-degrading enzymes. Production of these malicious virulence factors is controlled by interbacterial communication in a process known as quorum sensing. An increasing body of evidence reveals that the bacterial signal molecule N-(3-oxododecanoyl)-l-homoserine lactone (OdDHL) exhibits both quorum-sensing signalling and immune-modulating properties. Recently, yet another quorum-sensing signal molecule, the Pseudomonas quinolone signal (PQS), has been shown to affect cytokine release by mitogen-stimulated human T cells. In
the present article we demonstrate that both OdDHL and PQS decrease the production of interleukin-12 (IL-12) by
Escherichia coli lipopolysaccharide-stimulated bone marrow-derived dendritic cells (BM-DCs) without altering their IL-10
release. Moreover, BM-DCs exposed to PQS and OdDHL during antigen stimulation exhibit a decreased ability to induce
T-cell proliferation in vitro. Collectively, this suggests that OdDHL and PQS change the maturation pattern of stimulated
DCs away from a proinflammatory T-helper type I directing response, thereby decreasing the antibacterial activity of the
adaptive immune defence. OdDHL and PQS thus seem to possess dual activities in the infection process: as inducers of
virulence factors as well as immune-modulators facilitating the infective properties of this pathogen.

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Organisations: Department of Systems Biology, Division of Toxicology and Risk Assessment, Center for Biological
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Allergen specific responses in cord and adult blood are differentially modulated in the presence of endotoxins.
Background Endotoxins are common contaminants in allergen preparations and affect antigen-specific cellular responses. Distinct effects of endotoxin on cells in human umbilical cord and adult blood are poorly defined. Objectives To examine the effect of endotoxins in allergen preparations on cellular responses in human cord and peripheral blood (PB). Methods The endotoxin content in beta lactoglobulin (BLG), the peanut allergen Ara h 1 and the major birch pollen allergen Bet v 1 was assessed. Proliferation and cytokine response of mononuclear cells towards contaminated and lipopolysaccharide (LPS)-free allergens were evaluated at different time-points. Fractions of contaminated BLG were generated and assayed on their immuno-stimulatory capacity. The involvement of toll-like receptor (TLR) 2 and 4 was investigated by blocking antibodies and TLR-transfected human embryonic kidney cells. Results The proliferative response of cord blood (CB)-derived mononuclear cells towards allergen-preparations at day 3 was related to the level of LPS contamination. At day 7, proliferation was also detected in the absence of endotoxin. Cytokine production in CB was strongly affected by the content of endotoxin, TLR-4 dependent and not related to the allergen content. Allergen- and endotoxin-induced proliferative responses were generally significantly higher in CB than in adult blood. Conclusion Endotoxins in allergen preparations confound allergen-specific cellular responses. The impact of these contaminations varies with the blood source (CB vs PB) the., type of allergen and is time- and dose- dependent.

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Fedtsyrebalancen påvirker livsstilssygdomme og allergi

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Contributors: Jørgensen, S. B. (ed.), Hellgren, L., Pedersen, S. B.
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Fedtsyrebalance påvirker livsstilssygdomme og allergi

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Dietary fibres differentially modulate the bacterially induced maturation of dendritic cells

General information
Dietary fibres differentially modulate the TLR-induced maturation of dendritic cells

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General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Sørensen, R. B., Pedersen, S. B., Boye, M., Frøkiær, H.
Publication date: 2007

Event information
Event: Poster session presented at 13th International Congress of Immunology, Rio de Janeiro, Brazil.
Source-ID: 202255
Research output: Contribution to conference – Poster – Annual report year: 2007 – Research

Influence of gut microbiota on immunological maturation in infancy

General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Sørensen, R. B., Pedersen, S. B., Frøkiær, H.
Pages: 70-71
Publication date: 2007

Publication information
Journal: Annals of Nutrition and Metabolism
Volume: 51
ISSN (Print): 0250-6807
Ratings:
Influence of gut microbiota on immunological maturation in infancy

General information
Publication status: Published
Organisations: Department of Systems Biology, Division of Veterinary Diagnostics and Research, National Veterinary Institute
Contributors: Sørensen, R. B., Pedersen, S. B., Boye, M., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Yes
Event: Abstract from 13th International Congress of Immunology, Rio de Janeiro, Brazil.
Source: orbit
Source-ID: 202256
Research output: Contribution to conference → Conference abstract for conference – Annual report year: 2007 → Research → peer-review

Influence of gut microbiota on immunological maturation in infancy

General information
Publication status: Published
Organisations: Department of Systems Biology, Division of Veterinary Diagnostics and Research, National Veterinary Institute
Contributors: Sørensen, R. B., Pedersen, S. B., Boye, M., Frøkiær, H.
Publication date: 2007
Event information
Event: 10th European Nutrition Conference
Location: Paris, France
Source: orbit
Source-ID: 202254
Research output: Non-textual form → Sound/Visual production (digital) – Annual report year: 2007 → Research

Influence of gut microbiota on immunological maturation in infancy

General information
Publication status: Published
Organisations: Department of Systems Biology, Division of Veterinary Diagnostics and Research, National Veterinary Institute
Contributors: Sørensen, R. B., Pedersen, S. B., Boye, M., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Yes
Source: orbit
Source-ID: 202257
Research output: Contribution to conference → Poster – Annual report year: 2007 → Research → peer-review

Influence of gut microbiota on immunological maturation in infancy

Maturation and function of the immune system is highly influenced by the establishment of the microbiota in the gut, which in turn, particularly in infancy, is influenced by factors such as maternal microbiota and the environment, including diet. Studies have shown that although lymph nodes are able to elicit mixed Th1/Th2 responses, Th2 responses dominate in the spleen in the neonatal mouse. In this study, we compared phenotypic markers present on mesenteric lymph nodes (mLNs) and spleens from 3 weeks old mice, to levels found in adult mice. We found that mLNs displayed levels of CD4+ and CD8+ T-cells as well as NK-cells similar to those found in adult mice, while splenocytes expressed severely reduced levels of these markers and were impaired in their ability to proliferate in response to anti-CD3/anti-CD28. To further characterize the development of immunological maturation in spleens from young mice, female mice were administered different probiotics during pregnancy and lactation and their offspring sacrificed at the age of 3 weeks. Interestingly, intake of Bb. longum Q46 or E. coli Nissle 1917 resulted in reduced levels of CD4, CD8 and CD49b on the cell surface of
splenocytes as well as impaired ex vivo proliferative abilities of T lymphocytes as measured by 3H-TdR incorporation. Furthermore, Bb. longum Q46 and E. coli Nissle 1917 promoted a non-Th2 cytokine profile in splenocytes from offspring, and reduced cellular activation during ex vivo polyclonal stimulation. These results show that, although the maturation status of spleens, as representatives for the systemic immune system in mice aged 3 weeks, is quite low compared to mLNs, the maturation status and effector-function of spleens can be altered by administering probiotics during pregnancy.

General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Sørensen, R. B., Pedersen, S. B., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Yes
Source: orbit
Source-ID: 198824
Research output: Contribution to conference » Conference abstract for conference – Annual report year: 2007 » Research » peer-review

Kan kosten påvirke vores risiko for at udvikle allergi?

General information
Publication status: Published
Organisations: Unknown
Contributors: Pedersen, S. B., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Unknown

Publication information
Journal: Miljø og Sundhed
ISSN (Print): 1395-5241
Original language: Danish
Source: orbit
Source-ID: 194263
Research output: Contribution to journal » Journal article – Annual report year: 2007 » Communication

Proteome-analysis of gut bacteria-matured dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Pedersen, S. B., Kragh, M., Søndergaard, J. N., Bjerkan, L., Jacobsen, S., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Yes
Event: Poster session presented at Nutrigenomics in Denmark, Slagelse, Denmark.
Source: orbit
Source-ID: 199068
Research output: Contribution to conference » Poster – Annual report year: 2007 » Research » peer-review

Proteome-analysis of gut bacteria-matured dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Enzyme and Protein Chemistry, Technical University of Denmark
Contributors: Pedersen, S. B., Kragh, M., Søndergaard, J. N., Bjerkan, L., Jacobsen, S., Frøkiær, H.
Publication date: 2007
Peer-reviewed: Yes
Source: orbit
Source-ID: 199066
Research output: Contribution to conference » Poster – Annual report year: 2007 » Research » peer-review
The potential of gut bacteria-matured DCs to activate CD4+ T cells highly depends on the lipid composition of the T cell membrane

General information
Publication status: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Publication date: 2007

Event Information
Event: 10th European Nutrition Conference
Location: Paris, France
Source: orbit
Source-ID: 199067
Research output: Non-textual form › Sound/Visual production (digital) – Annual report year: 2007 » Research

Effects of dietary fatty acids on T-cell responses induced by dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology
Publication date: 2007
Peer-reviewed: Yes
Event: Poster session presented at LMC International Food Congress 2006, Copenhagen, Denmark.
Source: orbit
Source-ID: 199054
Research output: Contribution to conference › Poster – Annual report year: 2006 » Research » peer-review

Combinatorial effects of dietary fatty acids and probiotics on T-cell responses induced by dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology
Publication date: 2006
Peer-reviewed: Yes
Event: Poster session presented at LMC International Food Congress 2006, Copenhagen, Denmark.
Source: orbit
Source-ID: 199054
Research output: Contribution to conference › Poster – Annual report year: 2006 » Research » peer-review

Effects of dietary fatty acids on T-cell responses induced by dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology
Publication date: 2007
Peer-reviewed: Yes
Event: Poster session presented at LMC International Food Congress 2006, Copenhagen, Denmark.
Source: orbit
Source-ID: 199054
Research output: Contribution to conference › Poster – Annual report year: 2006 » Research » peer-review

Combinatorial effects of dietary fatty acids and probiotics on T-cell responses induced by dendritic cells

General information
Publication status: Published
Organisations: Department of Systems Biology
Publication date: 2006
Peer-reviewed: Yes
Event: Poster session presented at LMC International Food Congress 2006, Copenhagen, Denmark.
Source: orbit
Source-ID: 199054
Research output: Contribution to conference › Poster – Annual report year: 2006 » Research » peer-review
Dietary oil emulsions enhance the absorption of antive food allergens without effecting oral tolerance induction unless lipopolysaccharide is present

Effect of maternal dietary cow's milk on the immune response to beta-lactoglobulin in the offspring: A four generation study in mice

Evaluation of immune responses to food proteins in animal models requires that the animals are not already sensitized or orally tolerized against the proteins in question. Since maternal transfer of specific immune responses has been observed, breeding of animals on an antigen-free diet for several generations may be necessary to obtain immunologically naive animals. METHODS: To determine the most appropriate breeding conditions of mice to be used in immunological studies on food proteins, we examined immune responses towards beta-lactoglobulin (BLG) in mice bred on a milk-containing diet (F0) and then for three generations (F1-F3) on a commercially available milk-free diet. The specific antibody and cell-proliferative response to BLG was compared in non-immunized and immunized BALB/c mice, and in mice orally tolerized to BLG prior to immunization. RESULTS: The immune response to BLG in the F1 generation deviated from the response observed in the F0 and F2/F3 generations. Importantly, trace amounts of BLG detected in the commercial milk-free diet did not induce oral tolerance. CONCLUSIONS: The study showed that breeding mice on an antigen-free diet for at least two generations is required to attain animals appropriate for immunological studies of food proteins. Although the small quantity of BLG in the milk-free diet did not induce detectable oral tolerance in the present study, it is strongly recommended that the potential effect of contaminating dietary antigen is considered in future studies on food proteins. Copyright (c) 2005 S. Karger AG, Basel.
Effect of prior dietary exposure to cow's milk protein on antigen-specific and nonspecific cellular proliferation in mice

General information
Publication status: Published
Organisations: Enzyme and Protein Chemistry, Department of Systems Biology
Contributors: Pedersen, S. B., Magyar, O. H., Barkholt, V., Frøkiær, H.
Pages: 217-225
Publication date: 2005
Peer-reviewed: Yes

Publication information
Journal: Journal of Dairy Research
Volume: 72
ISSN (Print): 0022-0299
Ratings:
Scopus rating (2005): SJR 0.819 SNIP 1.097
Web of Science (2005): Indexed yes
Original language: English
Source: orbit
Source-ID: 184968

Milk-derived GM(3) and GD(3) differentially inhibit dendritic cell maturation and effector functionalities
Gangliosides are complex glycosphingolipids, which exert immune-modulating effects on various cell types. Ganglioside GD(3) and GM(3) are the predominant gangliosides of human breast milk but during the early phase of lactation, the content of GD(3) decreases while GM(3) increases. The biological value of gangliosides in breast milk has yet to be elucidated but when milk is ingested, dietary gangliosides might conceptually affect immune cells, such as dendritic cells (DCs). In this study, we address the in vitro effect of GD(3) and GM(3) on DC effector functionalities. Treatment of bone marrow-derived DCs with GD(3) before lipopolysaccharide-induced maturation decreased the production of interleukin-6 (IL-6), IL-10, IL-12 and tumor necrosis factor-alpha as well as reduced the alloreactivity in mixed leucocyte reaction (MLR). In contrast, only IL-10 and IL-12 productions were significantly inhibited by GM(3,) and the potency of DCs to activate CD4(+) cells in MLR was unaffected by GM(3). However, both gangliosides suppressed expression of CD40, CD80, CD86 and major histocompatibility complex class II on DCs. Because GD(3) overall inhibits DC functionalities more than GM(3), the immune modulating effect of the ganglioside fraction of breast milk might be more prominent in the commencement of lactation during which the milk contains the most GD(3).

General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Bronnum, H., Seested, T., Hellgren, L., Pedersen, S. B., Frokiaer, H.
Pages: 551-557
Publication date: 2005
Peer-reviewed: Yes

Publication information
Journal: Scandinavian Journal of Immunology
Volume: 61
Issue number: 6
ISSN (Print): 0300-9475
Ratings:
Scopus rating (2005): SJR 0.989 SNIP 0.641
Web of Science (2005): Indexed yes
Original language: English
DOIs:
10.1111/j.1365-3083.2005.01566.x
Source: orbit
Source-ID: 196297

Post-weaning maintenance of oral tolerance to β-lactoglobulin: the importance of antigen presence in the diet
Det vi spiser påvirker vores immunforsvar – men hvordan?

Dietary oil emulsions enhance the absorption of native food allergens without affecting oral tolerance induction unless lipopolysaccharide is present

Immune response in mice to ingested soya protein: antibody production, oral tolerance and maternal transfer

While allergic reactions to soya are increasingly investigated, the normal immune response to ingested soya is scarcely described. In the present study, we wanted to characterise the soya-specific immune response in healthy mice ingesting soya protein. Mice fed a soya-containing diet (F0) and mice of the first (F1) and second (F2) offspring generation bred on a soya protein-free diet were used either directly or were transferred between the soya-containing and soya protein-free diet during pregnancy or neonatal life. The mice were compared as to levels of naturally occurring specific antibodies analysed by ELISA, and to the presence of oral tolerance detected as a suppressed antibody and cell-proliferation response upon immunisation with soya protein. F0 mice generated soya-specific antibodies, while oral tolerance to the same soya proteins was also clearly induced. When F0 dams were transferred to soya protein-free feed before mating, the F1 and F2 offspring generations showed no significantly different response, indicating that soya-specific immune components were not maternally transmitted. However, the ingestion of dietary soya protein by F1 mice during late pregnancy and lactation caused a lasting antibody response in the offspring, but in this case in the absence of oral tolerance. This indicates that, under certain conditions, factors involved in spontaneous antibody production can be transmitted from mother to offspring. Understanding the immune response to soya protein ingested under healthy conditions is important in the assessment of adverse effects of soya protein and in the use of animal allergy models. The present results add to this understanding.
Lipopolysaccharide contamination of beta-lactoglobulin affects the immune response against intraperitoneally and orally administered antigen

Microbial components in the environment are potent activators of the immune system with capacity to shift the active immune response towards priming of Th1 and/or Th2 cells. Lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria, is extensively present in food products like cow’s milk. It is not well established, however, how this presence of LPS affects oral tolerance induction. Methods: We studied the effect of LPS contamination in a commercial preparation of the cow milk protein beta-lactoglobulin (beta-LG) on antigen-specific immune responses. IgG1/IgG2a production upon intraperitoneal immunization without adjuvant was measured, and oral tolerance induction against beta-LG was evaluated. Results: LPS contamination of beta-LG provoked a beta-LG-specific IgG2a response, as well as an enhanced beta-LG-specific IgG1 response upon intraperitoneal immunization. Oral tolerance induction to beta-LG was induced by aqueous solutions of beta-LG with and without LPS administration. Conversely, oral administration of w/o-emulsified beta-LG prevented oral tolerance to beta-LG only when the beta-LG was contaminated with LPS. Conclusions: LPS contamination of an aqueous protein solution does not affect oral tolerance induction, whereas LPS present in emulsion prevents oral tolerance induction towards the food protein.

Immunomodulatory effects induced by endotoxin present in some commercial β-lactoglobulin preparations

Microbial components in the environment are potent activators of the immune system with capacity to shift the active immune response towards priming of Th1 and/or Th2 cells. Lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria, is extensively present in food products like cow’s milk. It is not well established, however, how this presence of LPS affects oral tolerance induction. Methods: We studied the effect of LPS contamination in a commercial preparation of the cow milk protein beta-lactoglobulin (beta-LG) on antigen-specific immune responses. IgG1/IgG2a production upon intraperitoneal immunization without adjuvant was measured, and oral tolerance induction against beta-LG was evaluated. Results: LPS contamination of beta-LG provoked a beta-LG-specific IgG2a response, as well as an enhanced beta-LG-specific IgG1 response upon intraperitoneal immunization. Oral tolerance induction to beta-LG was induced by aqueous solutions of beta-LG with and without LPS administration. Conversely, oral administration of w/o-emulsified beta-LG prevented oral tolerance to beta-LG only when the beta-LG was contaminated with LPS. Conclusions: LPS contamination of an aqueous protein solution does not affect oral tolerance induction, whereas LPS present in emulsion prevents oral tolerance induction towards the food protein.
Immunostimulatory Potential of β-Lactoglobulin Preparations: Effects Caused by Endotoxin Contamination

Background: The immunomodulating potential residing in cow's milk proteins is currently receiving increasing attention because of growing interest in functional foods and the complex problem of cow's milk allergy. One of the major cow's milk allergens, whey protein beta-lactoglobulin, has previously been shown to mediate cellular activation in both human and murine immune cells. Objective: We examined the response to different beta-lactoglobulin preparations in naive immune cells. Methods: Splenocytes and cells from mesenteric lymph nodes derived from BALB/c mice bred and maintained on a milk-free diet were cultured in vitro with different beta-lactoglobulin preparations. Cell proliferation, cytokine production, and increases in intracellular glutathione were used as cellular activation markers. Moreover, the effect of beta-lactoglobulin on cytokine production in murine bone-marrow-derived dendritic cells was examined. Results: We observed that some commercial beta-lactoglobulin preparations induced pronounced proliferation of both spleen cells and cells from mesenteric lymph nodes; production of TNF-alpha, IL-6, IL-1beta, and IL-10; and an increased level of intracellular glutathione in spleen cell cultures. Furthermore, TNF-alpha, IL-6, IL-1beta, and IL-10 production was induced in murine bone-marrow-derived dendritic cells. Purification of beta-lactoglobulin from raw milk using nondenaturating conditions, however, revealed that the beta-lactoglobulin per se did not possess the immunomodulatory activity. Eventually, the immunostimulatory effect was found to be caused by endotoxin contamination. Conclusion: These results identify endotoxin as the main immunostimulatory component present in some commercial beta-lactoglobulin preparations. Moreover, the present study makes it evident that immunomodulatory effects attributed to beta-lactoglobulin need to be reassessed.

General information
Publication status: Published
Organisations: Department of Systems Biology, Enzyme and Protein Chemistry, Nestle
Contributors: Pedersen, S. B., Bovetto, L., Fritsche, R., Barkholt, V., Frøkiær, H.
Pages: 1216-1222
Publication date: 2003
Peer-reviewed: Yes

Abolishment of maternally induced oral tolerance to β-lactoglobulin in adult mice by feeding a milk-free diet from weaning

General information
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Johansen, S., Christensen, H. R., Barkholt, V., Frøkiær, H.
Publication date: 2001

Event information
Event: 8th International Symposium on Immunological, Chemical and Clinical Problems of Food Allergy
Location: Venezia, Italy
Source: orbit
Source-ID: 199060
Research output: Non-textual form – Annual report year: 2001 – Research
Influence of the diet on the specific immune response against soy proteins in mice

**General information**
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Christensen, H. R., Johansen, S., Frøkiær, H.
Publication date: 2001
Peer-reviewed: Yes
Event: Poster session presented at 8th International Symposium on Immunological, Chemical and Clinical Problems of Food Allergy, Venezia, Italy.
Source: orbit
Source-ID: 199062
Research output: Contribution to conference › Poster – Annual report year: 2001 › Research › peer-review

Transfer of tolerance to β-lactoglobulin from mothers to offspring: A four generation study in mice

**General information**
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Johansen, S., Christensen, H. R., Barkholt, V., Frøkiær, H.
Publication date: 2001
Peer-reviewed: Yes
Event: Poster session presented at 8th International Symposium on Immunological, Chemical and Clinical Problems of Food Allergy, Venezia, Italy.
Source: orbit
Source-ID: 199061
Research output: Contribution to conference › Poster – Annual report year: 2001 › Research › peer-review

Analysis of immuno-modulating capacity of peptides from bovine β-casein

**General information**
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Johansen, S., Barkholt, V., Frøkiær, H.
Publication date: 2000

**Event information**
Event: Milk Protein Conference
Location: Vinstra, Norway
Source: orbit
Source-ID: 199064
Research output: Non-textual form › Sound/Visual production (digital) – Annual report year: 2000 › Research

Characterisation of immunomodulating components in milk

**General information**
Publication status: Published
Organisations: Department of Systems Biology
Contributors: Pedersen, S. B.
Publication date: 2000

**Event information**
Event: Födoämnesallergi nätverk
Location: The Swedish Institute for Food and Biotechnology, Lund, Sweden
Source: orbit
Source-ID: 199063
Research output: Non-textual form › Sound/Visual production (digital) – Annual report year: 2000 › Research

Projects:
Structural and functional studies of MARCH5
Merklinger, L., PhD Student, Department of Systems Biology
Morth, J. P., Main Supervisor
Pedersen, S. B., Supervisor
auf dem Keller, U., Supervisor
01/01/2019 → 31/12/2021
Project: PhD

The influence of the gut microbiome on anti-cancer therapy
Xu, L., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Kristiansen, K., Supervisor
Stipendie fra uelandet
01/12/2017 → 30/11/2020
Award relations: The influence of the gut microbiome on anti-cancer therapy
Project: PhD

Systems Biology of the Infant Gut Microbiome
Myers, P. N., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Nielsen, H. B., Supervisor
Pedersen, A. G., Supervisor
Offentlig finansiering
01/10/2017 → 30/09/2020
Award relations: Systems Biology of the Infant Gut Microbiome
Project: PhD

Karakterisering af immun-modulerende komponenter i mælk
Pedersen, S. B., PhD Student, Department of Systems Biology
Frøkiær, H., Main Supervisor
Poulsen, L. K., Examiner
Husby, S., Examiner
Rasmussen, J. T., Examiner
Barkholt, V., Supervisor
Ansat eksternt CAMP
01/02/1999 → 30/09/2005
Award relations: Karakterisering af immun-modulerende komponenter i mælk
Project: PhD

Selective gut microbiome-immune interplays to identify major disease-driving bacteria and early life dynamics in microbiome establishment
Eriksen, C., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Arumugan, M., Supervisor
Kristiansen, K., Supervisor
Technical University of Denmark
15/03/2016 → 15/05/2019
Award relations: Selective gut microbiome-immune interplays to identify major disease-driving bacteria and early life dynamics in microbiome establishment
Project: PhD
Gut-microbiome-brain-axis signaling affecting pro-inflammatory cues and energy metabolism
Arora, P., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Kristiansen, K., Supervisor
Workman, C., Supervisor
Technical University of Denmark
15/01/2016 → 15/04/2019
Award relations: Gut-microbiome-brain-axis signaling affecting pro-inflammatory cues and energy metabolism
Project: PhD

Integrative Systems Immunology in Childhood Asthma
Wang, N., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Workman, C., Supervisor
Bønnelykke, K., Supervisor
Chawes, B. L. K., Supervisor
Bisgaard, H., Supervisor
Samfinansieret - Andet
15/12/2015 → 14/04/2019
Award relations: Integrative Systems Immunology in Childhood Asthma
Project: PhD

Characterization of novel non-invasive biomarkers for extracellular matrix remodeling in fibrosis and discovery of new targets for biomarker development
Nielsen, S. H., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Genovese, F., Supervisor
Leeming, D. J., Supervisor
auf dem Keller, U., Examiner
Miller, C., Examiner
Davies, M., Examiner
Eksternt finansieret virksomhed
01/03/2015 → 20/06/2018
Award relations: Characterization of novel non-invasive biomarkers for extracellular matrix remodeling in fibrosis and discovery of new targets for biomarker development
Project: PhD

Identification and Use of Biomarkers Reflecting Extracellular Matrix Remodeling in Cancer
Kehlet, S. N., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Karsdal, M. A., Supervisor
Qvist, P., Supervisor
Behrendt, N., Examiner
Erez, N., Examiner
Eksternt finansieret virksomhed
15/12/2014 → 14/01/2019
Award relations: Identification and Use of Biomarkers Reflecting Extracellular Matrix Remodeling in Cancer
Project: PhD

Development and Testing of Translational Ex Vivo Models for use in Drug Development in Inflammatory Osteoarthritis and Rheumatoid Arthritis
Kjelgaard-Petersen, C. F., PhD Student, Department of Systems Biology
Svensson, B., Main Supervisor
Bay-Jensen, A., Supervisor
Hägglund, P., Supervisor
Thudium, C. F., Supervisor
Pedersen, S. B., Examiner
van der Kraan, P., Examiner
Wenzel Kragstrup, T., Examiner
Eksternt finansieret virksomhed
01/11/2014 → 14/02/2018
Award relations: Development and Testing of Translational Ex Vivo Models for use in Drug Development in Inflammatory Osteoarthritis and Rheumatoid Arthritis
**Accelerating development of vaccines against cancer with pigs as a large animal model**
Overgaard, N. H., PhD Student, National Veterinary Institute
Jungersen, G., Main Supervisor
Andersen, M. H., Supervisor
Pedersen, S. B., Examiner
Golde, W. T., Examiner
Straten, P. T., Examiner
Forskningsrådsfinansiering
01/10/2014 → 31/01/2018
Award relations: Accelerating development of vaccines against cancer with pigs as a large animal model
Project: PhD

**A novel treatment for obesity and co-morbidities thereof**
Gydesen, S., PhD Student, Department of Systems Biology
Abou Hachem, M., Main Supervisor
Henriksen, K., Supervisor
Pedersen, S. B., Examiner
Kristiansen, K., Examiner
Lutz, T. A., Examiner
Eksternt finansieret virksomhed
01/04/2014 → 25/08/2017
Award relations: A novel treatment for obesity and co-morbidities thereof
Project: PhD

**Immune Recognition of Latency-instigating Pathogens by Human Dendritic Cells**
Søndergaard, J. N., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Lund, O., Examiner
De Jong, E. C., Examiner
Paludan, S. R., Examiner
Technical University of Denmark
01/01/2009 → 21/11/2012
Award relations: Immune Recognition of Latency-instigating Pathogens by Human Dendritic Cells
Project: PhD

**Transcriptomic analysis of human gut microbiome**
dos Santos, M. B. Q., PhD Student, Department of Systems Biology
Sicheritz-Pontén, T., Main Supervisor
Nielsen, H. B., Supervisor
Pedersen, S. B., Examiner
Walker, A., Examiner
Worning, P., Examiner
Anden EU-finansiering
01/10/2008 → 06/02/2013
Award relations: Transcriptomic analysis of human gut microbiome
Project: PhD

**Genomics based Simulation of the Immune System**
Hoof, I., PhD Student, Department of Systems Biology
Lund, O., Main Supervisor
Pedersen, S. B., Examiner
Bontrop, R. E., Examiner
Krogh, A. S., Examiner
Anden EU-finansiering
01/05/2006 → 01/07/2009
Award relations: Genomics based Simulation of the Immune System
Project: PhD
**Celle Biologiske studier af protease aktiverede liposomale drug delivery**
Johansen, P. T., PhD Student, Department of Micro- and Nanotechnology
Andresen, T. L., Main Supervisor
Jensen, S. S., Supervisor
Pedersen, S. B., Examiner
Fichtner, I., Examiner
Vogel, U. B., Examiner
Ansat eksternt
01/03/2008 → 19/04/2012
Award relations: Celle Biologiske studier af protease aktiverede liposomale drug delivery
Project: PhD

**Biomarkers and their use in age-related disease prediction - exploring risk factors for development of Alzheimer's disease**
Neergaard, J., PhD Student, Department of Systems Biology
Workman, C., Supervisor
Pedersen, S. B., Main Supervisor
Lund, O., Examiner
Christiansen, L., Examiner
Solomon, A., Examiner
Henriksen, K., Supervisor
Karsdal, M. A., Supervisor
Eksternt finansieret virksomhed
01/11/2013 → 25/08/2017
Award relations: Biomarkers and their use in age-related disease prediction - exploring risk factors for development of Alzheimer's disease
Project: PhD

**Biomarkers and their use in age-related disease prediction - exploring the relationship between obesity and type II diabetes**
Møller, K. D., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Beck-Nielsen, H., Supervisor
Henriksen, K., Supervisor
Karsdal, M. A., Supervisor
Hellgren, L., Examiner
Christensen, K., Examiner
Lind, L., Examiner
Technical University of Denmark
01/07/2013 → 15/02/2017
Award relations: Biomarkers and their use in age-related disease prediction - exploring the relationship between obesity and type II diabetes
Project: PhD

**Analysis of the T cell immune response in Yellow fever virus and HIV infections**
Frederiksen, J. W., PhD Student, Department of Systems Biology
Lund, O., Main Supervisor
Pedersen, S. B., Examiner
Sandberg, J. K., Examiner
Poulsen, S. D., Examiner
Technical University of Denmark
01/09/2012 → 15/12/2015
Award relations: Analysis of the T cell immune response in Yellow fever virus and HIV infections
Project: PhD

**Nutrigenomic Studies of Interactions between gut Microbiota, Enterocytes and the Immune System**
Kragh, M., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Hellgren, L., Supervisor
Lund, O., Examiner
Eiwegger, T., Examiner
Nielsen, D. S., Examiner
DTU-lønnet stipendie
01/07/2007 → 19/12/2014
Award relations: Nutrigenomic Studies of Interactions between gut Microbiota, Enterocytes and the Immune System
Project: PhD

**Immunomodulating Effects of Dietary Fibre**
Wismar, R., PhD Student, Department of Systems Biology
Pedersen, S. B., Supervisor
Svensson, B., Supervisor
Heegaard, P. M. H., Examiner
Lawther, J. M., Examiner
Brunak, S., Main Supervisor
Offentlig finansiering
01/01/2007 → 21/12/2010
Award relations: Immunomodulating Effects of Dietary Fibre
Project: PhD

**Improved nutritional Properties of dairy fat from cows feed green plant material - the role of peroxime Proliferator-activator receptor agonists**
Drachmann, T., PhD Student, Department of Systems Biology
Hellgren, L., Main Supervisor
Pedersen, S. B., Supervisor
Lundegaard, C., Examiner
Jensen, M. M., Examiner
Madsen, L., Examiner
Forskningsrådsfinansiering
01/04/2008 → 18/04/2012
Award relations: Improved nutritional Properties of dairy fat from cows feed green plant material - the role of peroxime Proliferator-activator receptor agonists
Project: PhD

**Prebiotics for Prevention of Gut Infections**
Sørensen, R. B., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Jungersen, G., Examiner
Pedersen, A. E., Examiner
Wick, M. J., Examiner
Forskningsrådsfinansiering
01/09/2007 → 23/05/2012
Award relations: Prebiotics for Prevention of Gut Infections
Project: PhD

**The role of fetal exposures to endotoxins in fetal programming of metabolic syndrome**
Ingvorsen, C., PhD Student, Department of Systems Biology
Hellgren, L., Main Supervisor
Pedersen, S. B., Supervisor
Nellemann, C., Examiner
Vaaq, A., Examiner
Zeyda, M., Examiner
Technical University of Denmark
01/06/2010 → 27/11/2013
Award relations: The role of fetal exposures to endotoxins in fetal programming of metabolic syndrome
Project: PhD

**Regulation of Host Metabolism by the Gut Microbiota**
Andersen, D., PhD Student, Department of Systems Biology
Hellgren, L., Main Supervisor
Pedersen, S. B., Supervisor
Lahl, K., Examiner
Frøkiær, H., Examiner
Zeyda, M., Examiner
Forskningsrådsfinansiering
01/10/2012 → 26/04/2017
Award relations: Regulation of Host Metabolism by the Gut Microbiota
Deciphering complex regulatory traits relating to host metabolism and immunity
Moll, J. M., PhD Student, Department of Systems Biology
Pedersen, S. B., Main Supervisor
Hellgren, L., Supervisor
Workman, C., Supervisor
Licht, T. R., Examiner
Clavel, T., Examiner
Paludan, S. R., Examiner
Technical University of Denmark
15/12/2012 → 15/02/2017
Award relations: Deciphering complex regulatory traits relating to host metabolism and immunity
Project: PhD

Extracellular matrix remodeling in cardiovascular and renal fibrosis
Nielsen, S. H., Project Participant, Department of Systems Biology, Center for Biological Sequence Analysis
Pedersen, S. B., Main Supervisor, Department of Systems Biology, Center for Biological Sequence Analysis
01/03/2015 → 28/02/2018
Project: Research

ProGI: Prebiotics for Prevention of Gastrointestinal Infections
Licht, T. R., Project Manager, National Food Institute
Wicks, A., Project Participant, National Food Institute
Bergström, A., Project Participant, National Food Institute
Andersen, J. B., Project Participant, National Food Institute
Poulsen, M., Project Participant, National Food Institute
Frøkiær, H., Project Manager, Department of Systems Biology
Pedersen, S. B., Project Manager, Department of Systems Biology
Forskningsrådene - Andre: DKK8,500,000.00
01/01/2007 → 01/09/2011
Award relations: Prebiotics for Prevention of Gastrointestinal Infections
Project: Research

NUTRIPEA
New technologies for improved and functional value of pea protein
Barkholt, V., Project Manager, Department of Biochemistry and Nutrition
Frøkiær, H., Project Participant, Department of Biochemistry and Nutrition
Nielsen, D., Project Participant, Department of Biochemistry and Nutrition
Follmann, F., Project Participant, Department of Biochemistry and Nutrition
Pedersen, S. B., Project Participant, Department of Biochemistry and Nutrition
Sørensen, A. D., Project Participant, Department of Biochemistry and Nutrition
Milora, N., Project Participant, Department of Biochemistry and Nutrition
Ukendt: DKK1,540,000.00
01/01/1996 → 31/12/1998
Collaborators: SIK, Semper AB, Swiss Federal Institute of Technology Zurich, ADRIA Food safety and Quality, VTT - Technical Research Centre of Finland, Provital
Award relations: NUTRIPEA
Project: Research

Characterization of immune stimulating components in milk
Milk contains components which are claimed to either stimulate or suppress immunological reactions. Enrichment of foods with an immune stimulating milk fraction may contribute to a higher health status. On the other hand, immunoactive components may contribute to development of food allergy. The aim of the project is identification and characterization of immunoactive components in milk. The project is closely related to "immune analyses".
Frøkiær, H., Project Manager, Department of Biochemistry and Nutrition
Barkholt, V., Project Participant, Department of Biochemistry and Nutrition
Pedersen, S. B., Project Participant, Department of Biochemistry and Nutrition
Nielsen, D., Project Participant, Department of Biochemistry and Nutrition
Ukendt: DKK3,000,000.00
01/01/1999 → 01/01/2002
Award relations: Characterization of immune stimulating components in milk
Project: Research

**PreGi - Prebiotics for Prevention of Gut Infections**

There is increasing evidence that (i) intestinal beneficial bacteria are selectively stimulated by ingestion of specific (prebiotic) carbohydrates, and that (ii) beneficial bacteria ingested as probiotics are capable of suppression of bacterial pathogens in the gut.

The idea of this project is to utilize existing animal models to identify dietary (prebiotic) carbohydrates that inhibit infection with selected pathogenic bacterial challengers.

Carbohydrates with the best potential for pathogen inhibition will then be further studied with respect to effects on beneficial gut bacteria, production of short-chain fatty acids (SCFAs), and immune modulation in the host animals.

Visualization of pathogenic challengers as well as of prebiotic-stimulated beneficial species in the intestinal environment will reveal whether an observed inhibition of a given pathogen results e.g. from competition for adhesion sites. The results obtained will be analyzed in a multivariate approach, in order to determine which of the above-mentioned factors have important impact on the anti-pathogen effect of prebiotics.

Poulsen, M., Project Participant, National Food Institute, Division of Microbiology and Risk Assessment
Wilcks, A., Project Participant, National Food Institute, Division of Microbiology and Risk Assessment
Bergström, A., Project Participant, National Food Institute, Division of Microbiology and Risk Assessment
Petersen, A., Project Participant, National Food Institute, Division of Microbiology and Risk Assessment
Ebersbach, T., Project Participant, National Food Institute, Division of Microbiology and Risk Assessment
Licht, T. R., Project Manager, National Food Institute, Division of Microbiology and Risk Assessment
Frukjær, H., Project Participant, University of Copenhagen
Pedersen, S. B., Project Participant, Department of Systems Biology
Serensen, R. B., Project Participant, Department of Systems Biology
Ouwehand, A., Project Participant, Danisco AS
Lahtinen, S., Project Participant, Danisco AS

01/01/2007 → 30/11/2010

Collaborators: Danisco AS, University of Copenhagen

**Activities:**

**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 committees, commissions, boards, councils, associations, organisations, or similar

**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

**Member of the Danish reference group for the EU-IMI program (External organisation)**

Period: 15 Dec 2015 → …

Susanne Brix Pedersen (Participant)
Department of Systems Biology
Department of Systems Biology
Center for Biological Sequence Analysis
Center for Biological Sequence Analysis

Description
Description
Member of the Danish reference group for the EU-IMI program
Member of the Danish reference group for the EU-IMI program
Body type: EU-IMI
Body type: EU-IMI

Related external organisation
Related external organisation
The Innovative Medicines Initiative
The Innovative Medicines Initiative
Activity: Membership › Membership of committees, commissions, boards, councils, associations, organisations, or similar
Activity: Membership › Membership of committees, commissions, boards, councils, associations, organisations, or similar

Panel member of Medical and Health Sciences under the National Research Council in Portugal (External organisation)
Panel member of Medical and Health Sciences under the National Research Council in Portugal (External organisation)
Period: 15 Nov 2015 → …
Period: 15 Nov 2015 → …
Susanne Brix Pedersen (Participant)
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Department of Systems Biology
Center for Biological Sequence Analysis
Center for Biological Sequence Analysis

Description
Description
Panel member of Medical and Health Sciences under the National Research Council in Portugal
Panel member of Medical and Health Sciences under the National Research Council in Portugal
Body type: FCT (National Research Council)
Body type: FCT (National Research Council)
Degree of recognition: International
Degree of recognition: International

Related external organisation
Related external organisation
Portugal National Research Council
Portugal National Research Council
Portugal
Portugal
Activity: Membership › Membership in review committee
Activity: Membership › Membership in review committee

InFLAME (External organisation)
InFLAME (External organisation)
Period: 12 Apr 2015 → …
Period: 12 Apr 2015 → …
Susanne Brix Pedersen (Participant)
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Department of Systems Biology
Center for Biological Sequence Analysis
Center for Biological Sequence Analysis

Description
Description
Body type: WUN
Body type: WUN
Degree of recognition: International
Degree of recognition: International

Related external organisation
Related external organisation
InFLAME
InFLAME

Cambridge University Press (External organisation)
Cambridge University Press (External organisation)
Period: 1 Jan 2011 → 31 Jan 2012
Period: 1 Jan 2011 → 31 Jan 2012
Susanne Brix Pedersen (Participant)
Susanne Brix Pedersen (Participant)
Department of Systems Biology
Department of Systems Biology
Center for Biological Sequence Analysis
Center for Biological Sequence Analysis

Description
Description
Editor for British Journal of Nutrition
Editor for British Journal of Nutrition
Body type: Journal
Body type: Journal
Degree of recognition: International
Degree of recognition: International

Related external organisation
Related external organisation
Cambridge University Press
Cambridge University Press
Press clippings:

The season of birth can influence the health of your child
Susanne Brix Pedersen
23/06/2016

Subject
www.klikk.no/foreldre/baby/immunforsvar-hos-baby-1678677.ece
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

The season of birth can influence the health of your child
23/06/2016
Foreldre.no, Web
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press/Media: Press / Media

Asthma-free with no hay fever? Thank your older sibling
Susanne Brix Pedersen
22/06/2016
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

Asthma-free with no hay fever? Thank your older sibling
22/06/2016
National Public Radio US, Web
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press/Media: Press / Media

Ny dansk forskning underbygger: Din fødselsmåned kan afgøre om du får gigt eller astma
Susanne Brix Pedersen
13/11/2015
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

Ny dansk forskning underbygger: Din fødselsmåned kan afgøre om du får gigt eller astma
13/11/2015
Ingeniøren, Print
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press/Media: Press / Media

The birth season influences your unborn childs immune response
Susanne Brix Pedersen
12/11/2015
Department of Systems Biology, Center for Biological Sequence Analysis

Media contribution (1)

The birth season influences your unborn childs immune response
12/11/2015
Politiken, Print
Susanne Brix Pedersen
Department of Systems Biology, Center for Biological Sequence Analysis
Press/Media: Press / Media