Early metastatic colorectal cancers show increased tissue expression of miR-17/92 cluster members in the invasive tumor front

Accurate prediction of regional lymph node metastases (LNM) in endoscopically resected pT1 colorectal cancer (CRC) is crucial in treatment stratification for subsequent radical surgery. Several miRNAs have been linked to CRC invasion and metastasis, including the oncogenic miR-17/92 cluster, and expression levels might have predictive value in the risk assessment of early metastatic progression in CRC. We performed global miRNA microarray using tissue samples from the invasive front of pT1 CRC and investigated associations of the miR-17/92 cluster and presence of LNM.

In total, 56 matched pT1 CRCs were thoroughly clinico-pathologically characterized and miRNA microarrays were performed on invasive front tissue samples. Global miRNA intensities were screened using paired t-tests between pT1pN+ and pT1pN0. Associations between miR-17/92 and histopathological features were analyzed using general linear models and tumor cell adjusted expression intensities.

miR-17-3p and miR-92a were significantly higher expressed in the invasive front of tumors with LNM compared to those without, corresponding to 1.53 fold higher expression of miR-17-3p (95%CI: 1.04–2.24, P = .030) and 1.28 fold higher expression of miR-92a (95%CI: 1.01–1.68, P = .042). An inverse association between miR-19a and presence of high grade tumor budding was observed (1.55 fold, 95%CI: 1.13–2.12, P = .008). We provide evidence for associations between early regional LNM and high expression levels of the miR-17/92 cluster members: miR-17-3p and miR-92a, in the invasive front of CRC. Our results support a role for the miR-17/92 cluster in early metastatic progression of CRC and calls for further investigation.
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Scopus rating (2013): CiteScore 2.91 SJR 1.472 SNIP 1.386
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BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 3.01 SJR 1.591 SNIP 1.478
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Protein from green biomass as a food resource

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Survey of 800+ datasets from human tissue and body fluid reveals XenomiRs are likely artifacts

miRNAs are small 22 nucleotide RNAs that can post-transcriptionally regulate gene expression. It has been proposed that dietary plant miRNAs can enter the human bloodstream and regulate host transcripts, however these findings have been widely disputed. We here conduct the first comprehensive meta-study in the field, surveying the presence and abundances of cross-species miRNAs (xenomiRs) in 824 sequencing datasets from various human tissues and body fluids. We find that xenomiRs are commonly present in tissues (17%) and body fluids (69%), however the abundances are low, comprising 0.001% of host human miRNA counts. Further, we do not detect a significant enrichment of xenomiRs in sequencing data originating from tissues and body fluids that are exposed to dietary intake (such as liver). Likewise, there is no significant depletion of xenomiRs in tissues and body fluids that are relatively separated from the main bloodstream (such as brain and cerebro-spinal fluids). Interestingly, the majority (81%) of body fluid xenomiRs stem from rodents, which are rare human dietary contributions, but common laboratory animals. Body fluid samples from the same studies tend to group together when clustered by xenomiR compositions, suggesting technical batch effects. Last, we performed carefully designed and controlled animal feeding studies, in which we detected no transfer of plant miRNAs into rat blood, or bovine milk sequences into piglet blood. In summary, our comprehensive computational and experimental results indicate that xenomiRs originate from technical artifacts rather than dietary intake.

General information

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Web of Science (2015): Impact factor 4.344
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The identification and functional annotation of RNA structures conserved in vertebrates

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

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A Systematic Comparison of Purification and Normalization Protocols for Quantitative MicroRNA Expressional Profiling in Insulin-Producing Cells

As microRNAs (miRs) are gaining increasing attention as key regulators of cellular processes, expressional quantification is widely applied. However, in the processing of relatively quantified data, the importance of testing the stability of several reference mRNAs and/or miRs and choosing among these for normalization is often overlooked, potentially leading to biased results. Here, we have optimized the purification of miR-enriched total RNA from pancreatic insulin-producing INS-1 cells. Additionally, we optimized and analyzed miR expression by a qPCR-based microarray and by specific qPCR and tested the stability of candidate reference mRNAs and miRs. Hence, this study gives a widely applicable example on how to easily and systematically test and decide how to normalize miR quantification. We suggest that caution in the interpretation of miR quantification studies that do not comprise stability analysis should be exerted.

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Scopus rating (2013): CiteScore 2.83 SJR 0.769 SNIP 1.103
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GLP-1 Induces Barrier Protective Expression in Brunner's Glands and Regulates Colonic Inflammation

Background: Beneficial roles for glucagon-like peptide 1 (GLP-1)/GLP-1R signaling have recently been described in diseases, where low-grade inflammation is a common phenomenon. We investigated the effects of GLP-1 in Brunner's glands and duodenum with abundant expression of GLP-1 receptors, as well as GLP-1 effect on colonic inflammation.

Methods: RNA from Brunner's glands of GLP-1R knockout and wild-type mice were subjected to full transcriptome profiling. Array results were validated by quantitative reverse transcription polymerase chain reaction in wild-type mice and compared with samples from inflammatory bowel disease (IBD) patients and controls. In addition, we performed a detailed investigation of the effects of exogenous liraglutide dosing in a T-cell driven adoptive transfer (AdTr) colitis mouse model.

Results: Analyses of the Brunner's gland transcriptomes of GLP-1R knockout and wild-type mice identified 722 differentially expressed genes. Upregulated transcripts after GLP-1 dosing included IL-33, chemokine ligand 20 (CCL20), and mucin 5b. Biopsies from IBD patients and controls, as well as data from the AdTr model, showed deregulated expression of GLP-1R, CCL20, and IL-33 in colon. Circulating levels of GLP-1 were found to be increased in mice with colitis. Finally, the colonic cytokine levels and disease scores of the AdTr model indicated reduced levels of colonic inflammation in liraglutide-dosed animals.

Conclusions: We demonstrate that IL-33, GLP-1R, and CCL20 are deregulated in human IBD, and that prophylactic treatment with 0.6 mg/kg liraglutide improves disease in AdTr colitis. In addition, GLP-1 receptor agonists upregulate IL-33, mucin 5b, and CCL20 in murine Brunner's glands. Taken together, our data indicate that GLP-1 receptor agonists affect gut homeostasis in both proximal and distal parts of the gut.
MicroRNAs as regulators of beta-cell function and dysfunction

In the last decade, there has been an explosion in both the number of and knowledge about miRNAs associated with both type 1 and type 2 diabetes. Even though we are presently in the initial stages of understanding how this novel class of posttranscriptional regulators are involved in diabetes, recent studies have demonstrated that miRNAs are important regulators of the islet transcriptome, controlling apoptosis, differentiation and proliferation, as well as regulating unique islet and beta-cell functions and pathways such as insulin expression, processing and secretion. Furthermore, a large number of miRNAs have been linked to diabetogenic processes induced by elevated levels of glucose, free fatty acids and inflammatory cytokines. Thus, miRNAs are novel therapeutic targets with the potential of protecting the beta-cell, and there is proof of principle that miRNA antagonists, so-called antagomirs, are effective in vivo for other disorders. miRNAs are exported out of cells in exosomes, raising the intriguing possibility of cell-to-cell communication between distant tissues via miRNAs and that miRNAs can be used as biomarkers of beta-cell function, mass and survival. The purpose of this review is to provide a status on how miRNAs control beta-cell function and viability in health and disease. Copyright (c) 2015 John Wiley & Sons, Ltd.
Regulation of miRNAs miR-30a and miR-143 in cerebral vasculature after experimental subarachnoid hemorrhage in rats

Background: miRNAs (miRNAs) are important regulators of translation and have been implicated in the pathogenesis of a number of cardiovascular diseases, including stroke, and suggested as possible prognostic biomarkers. Our aim was to identify miRNAs that are differentially regulated in cerebral arteries after subarachnoid hemorrhage (SAH), using a rat injection model of SAH and a qPCR-based screen of 728 rat miRNAs. Additionally, serum was analyzed for a possible spill-over to the circulation of regulated miRNAs from the vessel walls.

Results: We identified 482 different miRNAs expressed in cerebral arteries post-SAH. Two miRNAs, miR-30a and miR-143, were significantly upregulated in cerebral arteries after SAH compared to sham-operated animals. However, none of these exhibited significantly altered serum levels after SAH versus post-sham surgery. The most robust upregulation was seen for miR-143, which has several predicted targets and is a strong regulator of vascular morphology. We hypothesize that miR-30a and miR-143 may play a role in the vascular wall changes seen in post-SAH.

Conclusions: We report that miR-30a and miR-143 in the cerebral arteries show significant changes over time after SAH, but do not differ from sham-operated rats at 24 h post-SAH. Although this finding suggests interesting novel possible mechanisms involved in post-SAH cerebrovascular changes, the lack of regulation of these miRNAs in serum excludes their use as blood-borne biomarkers for cerebrovascular changes following SAH.
Regulation of microRNAs miR_30a and miR_143 in cerebral vasculature after experimental subarachnoid hemorrhage in rats.pdf

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Transcriptomic landscape of lncRNAs in inflammatory bowel disease

Background: Inflammatory bowel disease (IBD) is a complex multi-factorial inflammatory disease with Crohn's disease (CD) and ulcerative colitis (UC) being the two most common forms. A number of transcriptional profiling studies have provided compelling evidence that describe the role of protein-coding genes and microRNAs in modulating the immune responses in IBD. Methods: In the present study, we performed a genome-wide transcriptome profiling of IncRNAs and protein-coding genes in 96 colon pinch biopsies (inflamed and non-inflamed) extracted from multiple colonic locations from 45 patients (CD = 13, UC = 20, controls = 12) using an expression microarray platform. Results: In our study, we identified widespread dysregulation of IncRNAs and protein-coding genes in both inflamed and non-inflamed CD and UC compared to the healthy controls. In cases of inflamed CD and UC, we identified 438 and 745 differentially expressed IncRNAs, respectively, while in cases of the non-inflamed CD and UC, we identified 12 and 19 differentially expressed IncRNAs, respectively. We also observed significant enrichment (P-value < 0.001, Pearson's Chi-squared test) for 96 differentially expressed IncRNAs and 154 protein-coding genes within the IBD susceptibility loci. Furthermore, we found strong positive expression correlations for the intersecting and cis-neighboring differentially expressed IBD loci-associated IncRNA-protein-coding gene pairs. The functional annotation analysis of differentially expressed genes revealed their involvement in the immune response, pro-inflammatory cytokine activity and MHC protein complex. Conclusions: The IncRNA expression profiling in both inflamed and non-inflamed CD and UC successfully stratified IBD patients from the healthy controls. Taken together, the identified IncRNA transcriptional signature along with clinically relevant parameters suggest their potential as biomarkers in IBD.

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Circulating MicroRNAs in Plasma of Hepatitis B e Antigen Positive Children Reveal Liver-Specific Target Genes

Background and Aim. Hepatitis B e antigen positive (HBeAg-positive) children are at high risk of severe complications such as hepatocellular carcinoma and cirrhosis. Liver damage is caused by the host immune response to infected hepatocytes, and we hypothesise that specific microRNAs play a role in this complex interaction between virus and host. The study aimed to identify microRNAs with aberrant plasma expressions in HBeAg-positive children and with liver-

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specific target genes. Methods. By revisiting our previous screen of microRNA plasma levels in HBeAg-positive and HBeAg-negative children with chronic hepatitis B (CHB) and in healthy controls, candidate microRNAs with aberrant plasma expressions in HBeAg-positive children were identified. MicroRNAs targeting liver-specific genes were selected based on bioinformatics analysis and validated by qRT-PCR using plasma samples from 34 HBeAg-positive, 26 HBeAg-negative, and 60 healthy control children. Results. Thirteen microRNAs showed aberrant plasma expressions in HBeAg-positive children and targeted liver-specific genes. In particular, three microRNAs were upregulated and one was downregulated in HBeAg-positive children compared to HBeAg-negative and healthy control children, which showed equal levels. Conclusion. The identified microRNAs might impact the progression of CHB in children. Functional studies are warranted, however, to elucidate the microRNAs’ role in the immunopathogenesis of childhood CHB.

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CTSH regulates β-cell function and disease progression in newly diagnosed type 1 diabetes patients
Over 40 susceptibility loci have been identified for type 1 diabetes (T1D). Little is known about how these variants modify disease risk and progression. Here, we combined in vitro and in vivo experiments with clinical studies to determine how genetic variation of the candidate gene cathepsin H (CTSH) affects disease mechanisms and progression in T1D. The T allele of rs3825932 was associated with lower CTSH expression in human lymphoblastoid cell lines and pancreatic tissue. Proinflammatory cytokines decreased the expression of CTSH in human islets and primary rat β-cells, and overexpression of CTSH protected insulin-secreting cells against cytokine-induced apoptosis. Mechanistic studies indicated that CTSH exerts its antiapoptotic effects through decreased JNK and p38 signaling and reduced expression of the proapoptotic factors Bim, DP5, and c-Myc. CTSH overexpression also up-regulated Ins2 expression and increased insulin secretion. Additionally, islets from Cts4-/- mice contained less insulin than islets from WT mice. Importantly, the TT genotype was associated with higher daily insulin dose and faster disease progression in newly diagnosed T1D patients, indicating agreement between the experimental and clinical data. In line with these observations, healthy human subjects carrying the T allele have lower β-cell function, which was evaluated by glucose tolerance testing. The data provide strong evidence that CTSH is an important regulator of β-cell function during progression of T1D and reinforce the concept that candidate genes for T1D may affect disease progression by modulating survival and function of pancreatic β-cells, the target cells of the autoimmune assault.

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Genetic versus Non-Genetic Regulation of miR-103, miR-143 and miR-483-3p Expression in Adipose Tissue and Their Metabolic Implications-A Twin Study

Murine models suggest that the microRNAs miR-103 and miR-143 may play central roles in the regulation of subcutaneous adipose tissue (SAT) and development of type 2 diabetes (T2D). The microRNA miR-483-3p may reduce adipose tissue expandability and cause ectopic lipid accumulation, insulin resistance and T2D. We aimed to explore the genetic and non-genetic factors that regulate these microRNAs in human SAT, and to investigate their impact on metabolism in humans. Levels of miR-103, miR-143 and miR-483-3p were measured in SAT biopsies from 244 elderly monozygotic and dizygotic twins using real-time PCR. Heritability estimates were calculated and multiple regression analyses were performed to study associations between these microRNAs and measures of metabolism, as well as between these microRNAs and possible regulating factors. We found that increased BMI was associated with increased miR-103 expression levels. In addition, the miR-103 levels were positively associated with 2 h plasma glucose levels and hemoglobin A1c independently of BMI. Heritability estimates for all three microRNAs were low. In conclusion, the expression levels of miR-103, miR-143 and miR-483-3p in adipose tissue are primarily influenced by non-genetic factors, and miR-103 may be involved in the development of adiposity and control of glucose metabolism in humans.
miRNA profiles in cerebrospinal fluid from patients with central hypersomnias

MicroRNAs (miRNAs) are involved in the pathogenesis of many human diseases, including some neurological disorders. Recently, we have reported dysregulated miRNAs in plasma from patients with central hypersomnias including type I and type 2 narcolepsy, and idiopathic hypersomnia. This study addressed whether miRNA levels are altered in the cerebrospinal fluid (CSF) of patients with central hypersomnias. We conducted high-throughput analyses of miRNAs in CSF from patients using quantitative real-time polymerase chain reaction panels. We identified 13, 9, and 11 miRNAs with a more than two-fold change in concentration in CSF from patients with type 1 and type 2 narcolepsy and idiopathic hypersomnia, respectively, compared with matched healthy controls. Most miRNAs differed in more than one of the sleep disorders. However, all miRNAs were detected at low levels in CSF and varied between individuals. None of them showed significant differences in concentrations between groups after correcting for multiple testing, and none could be validated in an independent cohort. Nevertheless, approximately 60% of the most abundant miRNAs in the profile reported here have previously been identified in the CSF of healthy individuals, showing consistency with previous miRNA profiles found in CSF. In conclusion, we were not able to demonstrate distinct levels or patterns of miRNAs in CSF from central hypersomnia patients. (C) 2014 Elsevier B.V. All rights reserved.
miRNA Profiles in Plasma from Patients with Sleep Disorders Reveal Dysregulation of miRNAs in Narcolepsy and Other Central Hypersomnias

Study Objectives: MicroRNAs (miRNAs) have been implicated in the pathogenesis of human diseases including neurological disorders. The aim is to address the involvement of miRNAs in the pathophysiology of central hypersomnias including autoimmune narcolepsy with cataplexy and hypocretin deficiency (type 1 narcolepsy), narcolepsy without cataplexy (type 2 narcolepsy), and idiopathic hypersomnia.

Design: We conducted high-throughput analysis of miRNA in plasma from three groups of patients: type 1 narcolepsy, type 2 narcolepsy, and idiopathic hypersomnia, respectively, in comparison with healthy controls using quantitative real-time polymerase chain reaction (qPCR) panels.

Setting: University hospital based sleep clinic and research laboratories.

Patients: Twelve patients with type 1 narcolepsy, 12 patients with type 2 narcolepsy, 12 patients with idiopathic hypersomnia, and 12 healthy controls.

Measurements and Results: By analyzing miRNA in plasma with qPCR we identified 50, 24, and 6 miRNAs that were different in patients with type 1 narcolepsy, type 2 narcolepsy, and idiopathic hypersomnia, respectively, compared with healthy controls. Twenty miRNA candidates who fulfilled the criteria of at least two-fold difference and p-value <0.05 were selected to validate the miRNA changes in an independent cohort of patients. Four miRNAs differed significantly between type 1 narcolepsy patients and healthy controls. The miRNA differences were not specific for type 1 narcolepsy, since the levels of the four miRNAs were also altered in patients with type 2 narcolepsy and idiopathic hypersomnia compared with healthy controls.

Conclusion: The levels of four miRNAs differed in plasma from patients with type 1 narcolepsy, type 2 narcolepsy and idiopathic hypersomnia suggesting that alterations of miRNAs may be involved in the pathophysiology of central hypersomnias.
Spatially conserved regulatory elements identified within human and mouse Cd247 gene using high-throughput sequencing data from the ENCODE project

The Cd247 gene encodes for a transmembrane protein important for the expression and assembly of TCR/CD3 complex on the surface of T lymphocytes. Down-regulation of CD247 has functional consequences in systemic autoimmunity and...
has been shown to be associated with Type 1 Diabetes in NOD mouse. In this study, we have utilized the wealth of high-throughput sequencing data produced during the Encyclopedia of DNA Elements (ENCODE) project to identify spatially conserved regulatory elements within the Cd247 gene from human and mouse. We show the presence of two transcription factor binding sites, supported by histone marks and ChIP-seq data, that specifically have features of an enhancer and a promoter, respectively. We also identified a putative long non-coding RNA from the characteristically long first intron of the Cd247 gene. The long non-coding RNA annotation is supported by manual annotations from the GENCODE project in human and our expression quantification analysis performed in NOD and B6 mice using qRT-PCR. Furthermore, 17 of the 23 SNPs already known to be implicated with T1D were observed within the long non-coding RNA region in mouse. The spatially conserved regulatory elements identified in this study have the potential to enrich our understanding of the role of Cd247 gene in autoimmune diabetes. (C) 2014 Elsevier B.V. All rights reserved.
Temporal profiling of cytokine-induced genes in pancreatic β-cells by meta-analysis and network inference

Type 1 Diabetes (T1D) is an autoimmune disease where local release of cytokines such as IL-1β and IFN-γ contributes to β-cell apoptosis. To identify relevant genes regulating this process we performed a meta-analysis of 8 datasets of β-cell gene expression after exposure to IL-1β and IFN-γ. Two of these datasets are novel and contain time-series expressions in human islet cells and rat INS-1E cells. Genes were ranked according to their differential expression within and after 24 h from exposure, and characterized by function and prior knowledge in the literature. A regulatory network was then inferred from the human time expression datasets, using a time-series extension of a network inference method. The two most differentially expressed genes previously unknown in T1D literature (RIPK2 and ELF3) were found to modulate cytokine-induced apoptosis. The inferred regulatory network is thus supported by the experimental validation, providing a proof-of-concept for the proposed statistical inference approach. © 2014 Elsevier Inc.
Differential Plasma MicroRNA Profiles in HBeAg Positive and HBeAg Negative Children with Chronic Hepatitis B

Background and Aim: Children chronically infected with hepatitis B virus (HBV) are at high risk of progressive liver disease. However, no treatment is available that is consistently effective in curing chronic hepatitis B (CHB) in children. Improved understanding of the natural course of disease is warranted. Identification of specific microRNA (miRNA) profiles in children chronically infected with HBV may provide insight into the pathogenesis of CHB and lead to advances in the management of children with CHB.

Patients and Methods: MiRNA PCR panels were employed to screen plasma levels of 739 miRNAs in pooled samples from HBeAg positive, HBeAg negative, and healthy children. The three groups' plasma miRNA profiles were compared, and aberrantly expressed miRNAs were identified. The identified miRNAs were then validated. Individual RT-qPCRs were performed on plasma from 34 HBeAg positive, 26 HBeAg negative, and 60 healthy children. Results: A panel of 16 plasma miRNAs were identified as aberrantly expressed in HBeAg positive and HBeAg negative children (p

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Do post-translational beta cell protein modifications trigger type 1 diabetes?

Type 1 diabetes is considered an autoimmune disease characterised by specific T cell-mediated destruction of the insulin-producing beta cells. Yet, except for insulin, no beta cell-specific antigens have been discovered. This may imply that the autoantigens in type 1 diabetes exist in modified forms capable of specifically triggering beta cell destruction. In other immune-mediated diseases, autoantigens targeted by the immune system have undergone post-translational modification.
(PTM), thereby creating tissue-specific neo-epitopes. In a similar manner, PTM of beta cell proteins might create beta cell-specific neo-epitopes. We suggest that the current paradigm of type 1 diabetes as a classical autoimmune disease should be reconsidered since the immune response may not be directed against native beta cell proteins. A modified model for the pathogenetic events taking place in islets leading to the T cell attack against beta cells is presented. In this model, PTM plays a prominent role in triggering beta cell destruction. We discuss literature of relevance and perform genetic and human islet gene expression analyses. Both direct and circumstantial support for the involvement of PTM in type 1 diabetes exists in the published literature. Furthermore, we report that cytokines change the expression levels of several genes encoding proteins involved in PTM processes in human islets, and that there are type 1 diabetes-associated polymorphisms in a number of these. In conclusion, data from the literature and presented experimental data support the notion that PTM of beta cell proteins may be involved in triggering beta cell destruction in type 1 diabetes. If the beta cell antigens recognised by the immune system foremost come from modified proteins rather than native ones, the concept of type 1 diabetes as a classical autoimmune disease is open for debate.
Hepatitis B Surface Antigen Quantity Positively Correlates with Plasma Levels of microRNAs Differentially Expressed in Immunological Phases of Chronic Hepatitis B in Children

Background and Aim: Children with chronic hepatitis B (CHB) are at high risk of progressive liver disease. It is suggested that a newly-identified panel of 16 microRNAs is important in the pathogenesis of CHB in children. Subviral hepatitis B surface antigen (HBsAg) particles are produced in large excess over infectious virions. Interestingly, circulating HBsAg particles have been shown to carry microRNAs. A thorough characterisation of the identified microRNAs and HBsAg over time in plasma from children with CHB may provide useful information about the natural course of childhood CHB.

Patients and Methods: A cohort of 42 children with CHB was followed over time. Three to five blood samples were obtained from each child at minimum intervals of half a year; in total 180 blood samples. Plasma levels of the 16 microRNAs previously identified were analysed by quantitative real-time polymerase-chain-reaction. Plasma HBsAg was quantified using ARCHITECT (R) HBsAg assay.

Results: The presence of 14/16 plasma microRNAs in children with CHB was confirmed. All 14 microRNAs were significantly differentially expressed in different immunological phases of the disease. MicroRNA plasma levels were highest in immune-tolerant children, lower in immune-active children, and reached the lowest values in immune-inactive children.

General information
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Organisations: University of Copenhagen
This study aims to identify key miRNAs in circulation, which predict ongoing beta-cell destruction and regeneration in children with newly diagnosed Type 1 Diabetes (T1D). We compared expression level of sera miRNAs from new onset T1D children and age-matched healthy controls and related the miRNAs expression levels to beta-cell function and glycaemic control. Global miRNA sequencing analyses were performed on sera pools from two T1D cohorts (n = 275 and 129, resp.) and one control group (n = 151). We identified twelve upregulated human miRNAs in T1D patients (miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-26a, miR-27b, miR-25, miR-200a); several of these miRNAs were linked to apoptosis and beta-cell networks. Furthermore, we identified miR-25 as negatively associated with residual beta-cell function (est.: -0.12, P = 0.0037), and positively associated with glycaemic control (HbA1c) (est.: 0.11, P = 0.0035) 3 months after onset. In conclusion, this study demonstrates that miR-25 might be a "tissue-specific" miRNA for glycaemic control 3 months after diagnosis in new onset T1D children and therefore supports the role of circulating miRNAs as predictive biomarkers for tissue physiopathology and potential intervention targets.
Identification of Novel Type 1 Diabetes Candidate Genes by Integrating Genome-Wide Association Data, Protein-Protein Interactions, and Human Pancreatic Islet Gene Expression

Genome-wide association studies (GWAS) have heralded a new era in susceptibility locus discovery in complex diseases. For type 1 diabetes, >40 susceptibility loci have been discovered. However, GWAS do not inevitably lead to identification of the gene or genes in a given locus associated with disease, and they do not typically inform the broader context in which the disease genes operate. Here, we integrated type 1 diabetes GWAS data with protein-protein interactions to construct biological networks of relevance for disease. A total of 17 networks were identified. To prioritize and substantiate these networks, we performed expression profiling in human pancreatic islets exposed to proinflammatory cytokines. Three networks were significantly enriched for cytokine-regulated genes and, thus, likely to play an important role for type I diabetes in pancreatic islets. Eight of the regulated genes (CD83, IFNGR1, IL17RD, TRAF3IP2, IL27RA, PLCG2, MYO1B, and CXCR7) in these networks also harbored single nucleotide polymorphisms nominally associated with type 1 diabetes. Finally, the expression and cytokine regulation of these new candidate genes were confirmed in insulin-secreting INS-1 beta-cells. Our results provide novel insight to the mechanisms behind type 1 diabetes pathogenesis and, thus, may provide the basis for the design of novel treatment strategies. Diabetes 61:954-962, 2012
Huntingtin-interacting protein 14 is a type 1 diabetes candidate protein regulating insulin secretion and β-cell apoptosis

Type 1 diabetes (T1D) is a complex disease characterized by the loss of insulin-secreting β-cells. Although the disease has a strong genetic component, and several loci are known to increase T1D susceptibility risk, only few causal genes have currently been identified. To identify disease-causing genes in T1D, we performed an in silico "phenome–interactome analysis" on a genome-wide linkage scan dataset. This method prioritizes candidates according to their physical interactions at the protein level with other proteins involved in diabetes. A total of 11 genes were predicted to be likely disease genes in T1D, including the INS gene. An unexpected top-scoring candidate gene was huntingtin-interacting protein (HIP)-14/ZDHHC17. Immunohistochemical analysis of pancreatic sections demonstrated that HIP14 is almost exclusively expressed in insulin-positive cells in islets of Langerhans. RNAi knockdown experiments established that HIP14 is an antiapoptotic protein required for β-cell survival and glucose-stimulated insulin secretion. Proinflammatory cytokines (IL-1β and IFN-γ) that mediate β-cell dysfunction in T1D down-regulated HIP14 expression in insulin-secreting INS-1 cells and in isolated rat and human islets. Overexpression of HIP14 was associated with a decrease in IL-1β–induced NF-κB activity and protection against IL-1β–mediated apoptosis. Our study demonstrates that the current network biology approach is a valid method to identify genes of importance for T1D and may therefore embody the basis for more rational and targeted therapeutic approaches.

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BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 8.84 SJR 6.814 SNIP 2.691
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 8.86 SJR 6.898 SNIP 2.734
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 9.5 SJR 7.073 SNIP 2.738
Independent component and pathway-based analysis of miRNA-regulated gene expression in a model of type 1 diabetes

BACKGROUND: Several approaches have been developed for miRNA target prediction, including methods that incorporate expression profiling. However, the methods are still in need of improvements due to a high false discovery rate. So far, none of the methods have used independent component analysis (ICA). Here, we developed a novel target prediction method based on ICA that incorporates both seed matching and expression profiling of miRNA and mRNA expressions. The method was applied on a cellular model of type 1 diabetes.

RESULTS: Microrray profiling identified eight miRNAs (miR-124/128/192/194/204/375/672/708) with differential expression. Applying ICA on the mRNA profiling data revealed five significant independent components (ICs) correlating to the experimental conditions. The five ICs also captured the miRNA expressions by explaining >97% of their variance. By using ICA, seven of the eight miRNAs showed significant enrichment of sequence predicted targets, compared to only four miRNAs when using simple negative correlation. The ICs were enriched for miRNA targets that function in diabetes-relevant pathways e.g. type 1 and type 2
diabetes and maturity onset diabetes of the young (MODY). CONCLUSIONS: In this study, ICA was applied as an attempt to separate the various factors that influence the mRNA expression in order to identify miRNA targets. The results suggest that ICA is better at identifying miRNA targets than negative correlation. Additionally, combining ICA and pathway analysis constitutes a means for prioritizing between the predicted miRNA targets. Applying the method on a model of type 1 diabetes resulted in identification of eight miRNAs that appear to affect pathways of relevance to disease mechanisms in diabetes.

**General information**

State: Published
Organisations: Department of Systems Biology, Steno Diabetes Centre, University of Copenhagen, Copenhagen University Hospital
Contributors: Bang-Berthelsen, C. H., Pedersen, L., Fløyel, T., Hagedorn, P., Gylvin, T., Pociot, F.
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Web of Science (2017): Indexed yes
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Web of Science (2016): Impact factor 3.729
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Scopus rating (2015): CiteScore 4.3 SJR 2.348 SNIP 1.159
Web of Science (2015): Impact factor 3.867
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 4.18 SJR 2.327 SNIP 1.199
Web of Science (2014): Impact factor 3.986
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High Glucose Suppresses Human Islet Insulin Biosynthesis by Inducing miR-133a Leading to Decreased Polypyrimidine Tract Binding Protein Expression

Background: Prolonged periods of high glucose exposure results in human islet dysfunction in vitro. The underlying mechanisms behind this effect of high glucose are, however, unknown. The polypyrimidine tract binding protein (PTB) is required for stabilization of insulin mRNA and the PTB mRNA 3'-UTR contains binding sites for the microRNA molecules miR-133a, miR-124a and miR-146. The aim of this study was therefore to investigate whether high glucose increased the levels of these three miRNAs in association with lower PTB levels and lower insulin biosynthesis rates.

Methodology/Principal Findings: Human islets were cultured for 24 hours in the presence of low (5.6 mM) or high glucose (20 mM). Islets were also exposed to sodium palmitate or the proinflammatory cytokines IL-1 beta and IFN-gamma, since saturated free fatty acids and cytokines also cause islet dysfunction. RNA was then isolated for real-time RT-PCR analysis of miR-133a, miR-124a, miR-146, insulin mRNA and PTB mRNA contents. Insulin biosynthesis rates were determined by radioactive labeling and immunoprecipitation. Synthetic miR-133a precursor and inhibitor were delivered to dispersed islet cells by lipofection, and PTB was analyzed by immunoblotting following culture at low or high glucose. Culture in high glucose resulted in increased islet contents of miR-133a and reduced contents of miR-146. Cytokines increased the contents of miR-146. The insulin and PTB mRNA contents were unaffected by high glucose. However, both PTB protein levels and insulin biosynthesis rates were decreased in response to high glucose. The miR-133a inhibitor prevented the high glucose-induced decrease in PTB and insulin biosynthesis, and the miR-133a precursor decreased PTB levels and insulin biosynthesis similarly to high glucose.

Conclusion: Prolonged high-glucose exposure down-regulates PTB levels and insulin biosynthesis rates in human islets by increasing miR-133a levels. We propose that this mechanism contributes to hyperglycemia-induced beta-cell dysfunction.
Novel monoclonal antibodies against Pdx1 reveal feedback regulation of Pdx1 protein levels

The aim of this study was to characterize two monoclonal antibodies (F6A11 and F109-D12) generated against Pdx1 (pancreatic and duodenal homeobox-1), a homeodomain transcription factor, which is critical for pancreas formation as well as for normal pancreatic beta cell function. For production of monoclonal antibodies, we immunized Robertsonian POSF (RBF)mice with a GST-Pdx1 fusion protein containing a 68-amino acid C-terminal fragment of rat Pdx1. These monoclonal antibodies detect Pdx1 by western blotting and allow immunohistochemical detection of Pdx1 in both mouse and rat tissue. F6A11 and F109-D12 produce IHC staining patterns indistinguishable from that obtained with highly specific polyclonal Pdx1 antisera raised in rabbits and goats, when applied to embryonic or adult mouse pancreatic tissue. In contrast to previously generated polyclonal anti-Pdx1 antisera, we also demonstrate that F6A11 works for intracellular fluorescence activated cell sorting (FACS) staining of Pdx1. By using F6A11, we characterize the induction of Pdx1 in the Doxycycline (DOX) inducible insulinoma cell line INSr alpha beta-Pdx1 and follow the reduction of Pdx1 after removing Dox. Finally, we show that induction of exogenous Pdx1 leads to a reduction in endogenous Pdx1 levels, which suggests that a negative feedback loop is involved in maintaining correct levels of Pdx1 in the cell.
Zinc transporter gene expression is regulated by pro-inflammatory cytokines: a potential role for zinc transporters in beta-cell apoptosis?

Background: beta-cells are extremely rich in zinc and zinc homeostasis is regulated by zinc transporter proteins. beta-cells are sensitive to cytokines, interleukin-1 beta (IL-1 beta) has been associated with beta-cell dysfunction and -death in both type 1 and type 2 diabetes. This study explores the regulation of zinc transporters following cytokine exposure.Methods: The effects of cytokines IL-1 beta, interferon-gamma (IFN-gamma), and tumor necrosis factor-alpha (TNF-alpha) on zinc transporter gene expression were measured in INS-1-cells and rat pancreatic islets. Being the more sensitive transporter, we further explored ZnT8 (Slc30A8): the effect of ZnT8 over expression on cytokine induced apoptosis was investigated as well as expression of the insulin gene and two apoptosis associated genes, BAX and BCL2.Results: Our results showed a dynamic response of genes responsible for beta-cell zinc homeostasis to cytokines: IL-1 beta down regulated a number of zinc-transporters, most strikingly ZnT8 in both islets and INS-1 cells. The effect was even more pronounced when mixing the cytokines. TNF-alpha had little effect on zinc transporter expression. IFN-gamma down regulated a number of zinc transporters. Insulin expression was down regulated by all cytokines. ZnT8 over expressing cells were more sensitive to IL-1 beta induced apoptosis whereas no differences were observed with IFN gamma, TNF-alpha, or a mixture of cytokines.Conclusion: The zinc transporting system in beta-cells is influenced by the exposure to cytokines. Particularly ZnT8, which has been associated with the development of diabetes, seems to be cytokine sensitive.
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Web of Science (2015): Impact factor 1.739
Scopus rating (2014): CiteScore 2.23 SJR 0.754 SNIP 0.892
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Projects:

Evaluering af risikoen ved indtagelse af græs-juice/-ekstrakt - en potentiel fremtidig protein kilde
Formålet med projektet er at få videnskabelig evidens for om rajgræs kan benyttes som en ny fædevare uden øget risiko for inducering af allergiske reaktioner, dette enter ved de novo sensibilisering eller ved krydsreaktioner i individer med
Production of therapeutic proteins in Lactococcus lactis
Xiao, H., PhD Student, National Food Institute
Jensen, P. R., Main Supervisor, National Food Institute
Bang-Berthelsen, C. H., Supervisor, National Food Institute
Solem, C., Supervisor, National Food Institute
Stipendie fra udlændet
01/12/2017 → 30/11/2020
Award relations: Production of therapeutic proteins in Lactococcus lactis
Project: PhD

ALLEVIADE: ALLEVIADE - A novel strategy for food allergy prevention and treatment
Food allergy is an adverse effect to otherwise harmless proteins in the food, whereas oral tolerance is the default result from ingestion of food proteins. Food allergy is a major health problem of growing concern, affecting ~5-8% of young children and 2-4% of adults. No reliable strategy exists for prevention and treatment of food allergy, and strict avoidance of the offending food is presently the only viable management option. Living with food avoidance has a huge impact on the quality of life of food allergic patients, with daily fear of serious or even fatal reactions. The need for efficient methods for prevention and treatment is therefore evident and urgent. The purpose of the project is to develop methods to prevent and treat food allergy using a novel strategy, recently invented. Our vision is to overcome limitations in current strategies for food allergy prevention and treatment; being efficient without inducing allergic reactions. The specific goals of the project are: 1)To develop protein ingredients for a new generation of hypoallergenic (HA) infant formulas (IF) for cow’s milk allergy (CMA) prevention 2)To develop a drug candidate for use in immunotherapy (IT) for peanut allergy (PA) treatment These products would have the capacity to enhance the quality of life for millions of patients in risk of developing CMA and of patients with an already established PA. The market potential is great for both product categories. In addition, the newly developed strategy may form the basis for prevention, treatment and diagnostic products targeting other food allergies.
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Sancho Vega, A. I., Project Participant, National Food Institute
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Collaborators: University of Leeds, Arla Foods Ingredients Group P/S, Medical University of Vienna, University of Toronto
Project: Research

Press clippings:

MikroRNA fra fødevarer kan ikke overføres til mennesker
Claus Heiner Bang-Berthelsen
29/03/2017
National Food Institute, Research Group for Microbial Biotechnology and Biorefining

Media coverage (1)

MikroRNA fra fødevarer kan ikke overføres til mennesker
29/03/2017
ScienceNordic (International), Denmark, Web
Catherine Jex
http://sciencenordic.com/can-microrna-food-harm-us-no-say-scientists
Claus Heiner Bang-Berthelsen
MikroRNA fra fødevarer kan ikke overføres til mennesker
Claus Heiner Bang-Berthelsen
22/02/2017
National Food Institute, Research Group for Microbial Biotechnology and Biorefining

Media contribution (1)

MikroRNA fra fødevarer kan ikke overføres til mennesker
22/02/2017
Videnskab.dk, Web
Kristian Peter Sjøgren
http://videnskab.dk/krop-sundhed/kan-mikrorna-i-maden-skade-os-nej-siger-forskere
Claus Heiner Bang-Berthelsen
National Food Institute, Research Group for Microbial Biotechnology and Biorefining

Media contribution (1)