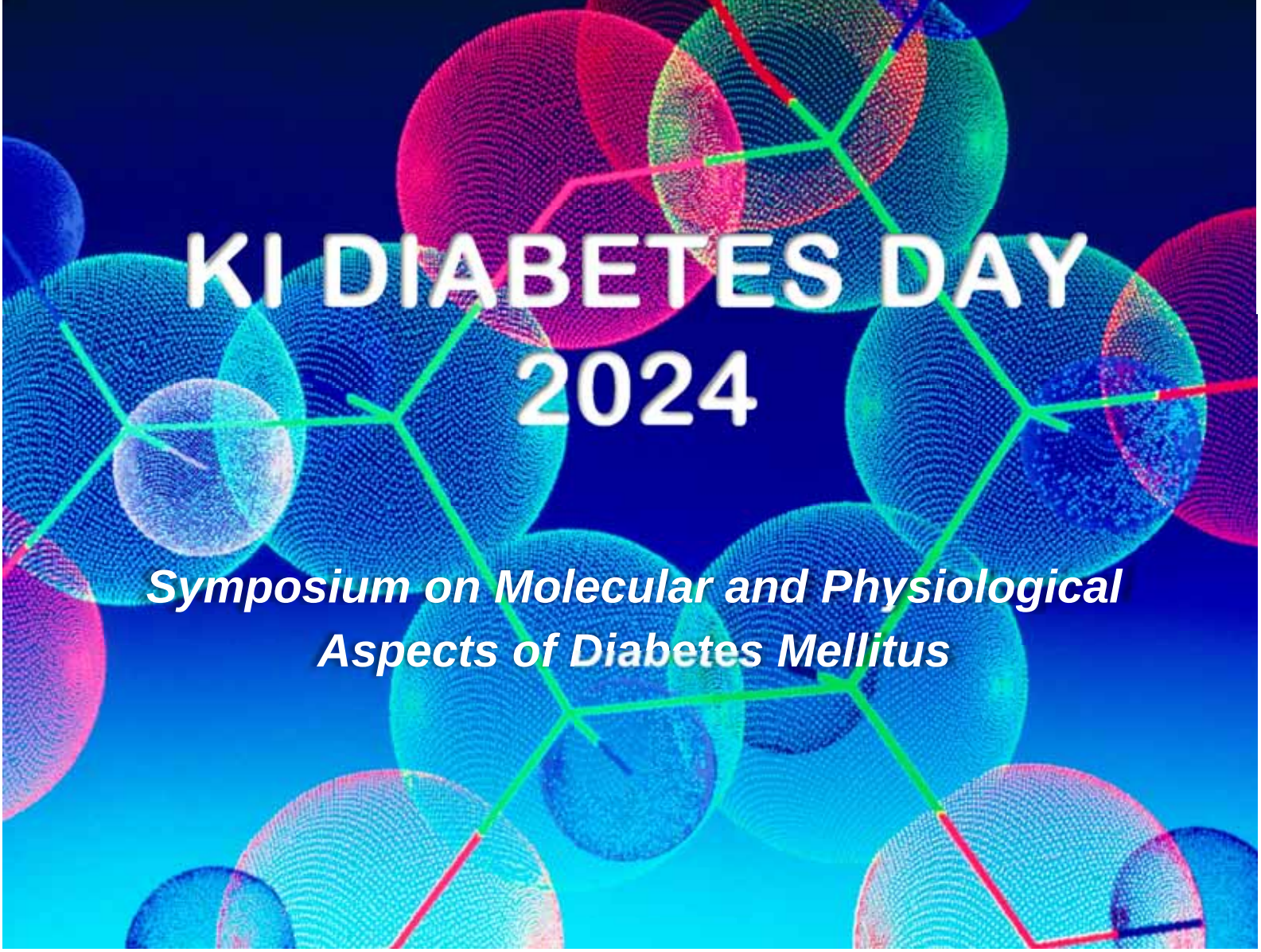

November 14, 2024 | Karolinska Institutet

PROGRAMME & ABSTRACTS

world diabetes day

SRP DIABETES

Karolinska Institutet

Organiser:

Strategic Research Programme in Diabetes at Karolinska Institutet (SRP Diabetes).

https://ki.se/en/srp-diabetes

SRP Diabetes is an integrated research environment in the diabetes and metabolism area with some 400 affiliated researchers at both Karolinska Institutet and Umeå University. Results are translated between basic and clinical science with the aim to improve both prevention, care and treatment of people with diabetes.

Specifically, SRP Diabetes activities aim to:

- Develop and support technical platforms important for researchers at KI and UmU. These platforms include a Metabolic Phenotyping Centre for Diabetic Animal Models, a Centre for Clinical Metabolic Research in Diabetes, Beta Cell in-vivo Imaging/ Extracellular Flux Analysis (Seahorse) and Spatial Transcriptomics.
- Support for critical instrumentation to group leaders
- Support the next generation of scientist: postdoctoral fellowship program
- Increase interactions between the research teams of the programme by supporting collaborative projects and arranging common symposia, meetings and seminars
- Support undergraduate and graduate education within the research areas connected to the programme
- Increase translational research by supporting collaborative projects between experimental and clinical researchers
- Facilitate international contacts
- Support interactions with the biotech and pharmaceutical industry
- Support innovation and commercial utilization by liasing with Karolinska Institutet Innovations
- Increase public awareness and inform about current diabetes related research

The programme coordinates laboratories possessing substantial expertise and unique technical resources, thus affording a natural point of contact for collaboration within the diabetes area, both for researchers within Karolinska Institutet and Umeå University as well as with external researchers.

SRP Diabetes Management:

Director: Anna Krook (Karolinska Institutet)

Vice-Director: Mikael Rydén (Karolinska Institutet)

Olov Andersson (Karolinska Institutet)

Helena Edlund (Umeå University)

Malin Flodström Tullberg (Karolinska Institutet)

Carolina Hagberg (Karolinska Institutet)

Thomas Nyström (Karolinska Institutet)

Harriet Wallberg (Karolinska Institutet)

Venue: Eva and Georg Klein Hall, Biomedicum, Karolinska Institutet, Solna

Web: https://ki.se/en/srp-diabetes/diabetes-day

Programme

08:30 – 09:00	REGISTRATION
09:00 - 09:10	Welcome Note: **Anna Krook**

SESSION 1	Pancreatic islet pathophysiology in diabetes	Chair: Helena Edlund

09:10 - 09:45	"RNA editing deficiency as a path to islet inflammation and diabetes" **Yuval Dor,** *The Hebrew University of Jerusalem*
09:45 - 10:20	"Genome-wide genetic convergence of RFX6 biology in early-stage type 2 diabetes" **Marcela Brissova,** *Vanderbilt University*
10:20 - 10:50	COFFEE BREAK

SESSION 2	Human genetics and omics of diabetes	Chair: Harriet Wallberg

10:50 - 11:25	"How does human functional genetics of rare variants illuminate diabetes pathophysiology?" **Amélie Bonnefond,** *EGID/Université de Lille*
11:25 - 12:00	"Multi-omic risk factors in ageing populations with a focus on diabetes" **Amy Jayne McKnight**, *Queens University Belfast*
12:00 - 13:00	LUNCH (Posters to be mounted)

SESSION 3	Life style factors and metabolic disease	Chair: Thomas Nyström

13:00 - 13:35	"The interplay between diet, metabolomics, and cardiometabolic diseases: towards precision nutrition" **Marta Guasch-Ferré,** *University of Copenhagen*
13:35 - 14:10	"Opportunities and challenges in understanding diabetes pathophysiology in Africa: Insights from T2DM cohorts with low prevalence of common risk factors in Africa" **Fredirick Mashili,** *Muhimbili University*
14:10 - 14:40	COFFEE BREAK

SESSION 4	Disease causing metabolic pathways	Chair: Mikael Rydén

14:40 - 15:15	"Auto- and paracrine sensing of succinate as a metabolic stress signal by SUCNR1/GPR91 in adipose, muscle, liver and kidney" **Thue Schwartz**, *University of Copenhagen*
15:15 - 15:50	"Amino acid and sphingolipid metabolism in co-morbidities of diabetes" **Christian Metallo,** *Salk Institute*
15:50 - 16:00	Closing Remarks: **Mikael Rydén**

POSTER SESSION, Drinks and light bites	

16.00-18.00	Drinks and light bites served in the foyer by the entrance
16.15-16.45	Posters with odd numbers will be presented
16.45-17.15	Posters with even numbers will be presented

Speaker abstracts

SESSION 1

RNA editing deficiency as a path to islet inflammation and diabetes

Yuval Dor

The Hebrew University of Jerusalem, Israel

A major hypothesis for the etiology of type 1 diabetes (T1D) postulates initiation by viral infection, leading to double-stranded RNA (dsRNA)-mediated interferon response and inflammation; however, a causal virus has not been identified. We have used a mouse model, corroborated with human islet data, to demonstrate that endogenous dsRNA in beta cells can lead to a diabetogenic immune response, thus identifying a virus-independent mechanism for T1D initiation. We found that disruption of the RNA editing enzyme ADAR in beta cells triggers a massive interferon response, islet inflammation and beta cell failure and destruction, with features bearing striking similarity to early-stage human T1D. Glycolysis via calcium enhances the interferon response, suggesting an actionable vicious cycle of inflammation and increased beta cell workload. Thus, defects in RNA editing in beta cell may lead to the accumulation of endogenous dsRNA and to islet inflammation and diabetes. I will present published and unpublished data supporting the hypothesis that defects in RNA editing contribute to early stages of T1D.

Speaker abstracts

Genome-wide genetic convergence of RFX6 biology in early-stage type 2 diabetes

Marcela Brissova

Director, Islet and Pancreas Analysis Core, Director, Human Islet Phenotyping Program of IIDP, Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt University, 2213 Garland Avenue, 8435G MRB IV Nashville, TN 37232

Type 2 diabetes mellitus (T2D) genome-wide association studies (GWAS) have identified hundreds of signals in non-coding and beta cell regulatory genomic regions, but deciphering their biological mechanisms remains challenging. In this collaborative effort, we integrated diverse multimodal analyses across pancreatic tissues and islets of early-stage T2D and control donors from the Vanderbilt Pancreas Biorepository and other resources, including the Integrated Islet Distribution Program, Human Pancreas Analysis Program, and Alberta Diabetes Institute IsletCore. We show that this stage of T2D is characterized by beta cell-intrinsic defects that can be proportioned into gene regulatory modules with enrichment in signals of genetic risk. Within one such module, we discovered the beta cell hub gene and transcription factor *RFX6*. Perturbation of *RFX6* in primary human islet cells alters beta cell chromatin architecture at regions enriched for T2D GWAS signals. We have combined this single-cell data with population-scale genetic data from the UK Biobank European-ancestry cohort, which includes nearly half a million individuals. Our findings robustly show that various levels of common genetic variation converge on a regulatory network controlled by *RFX6*. Disruption of this network is causally linked to an elevated T2D risk and results in beta cell dysfunction in the early stages of T2D. Understanding the molecular mechanisms of complex, systemic diseases necessitates the integration of signals from multiple molecules, cells, organs, and individuals. Our collaborative approach will be a useful template to identify and validate key regulatory networks and master hub genes for other diseases or traits with GWAS data, fostering a sense of inclusion and shared purpose within the scientific community.

Speaker abstracts

SESSION 2

How does human functional genetics of rare variants illuminate diabetes pathophysiology?

Amélie Bonnefond

EGID/Université de Lille

Diabetes ranks among the leading causes of mortality and disability worldwide, with a significant economic burden that affects healthcare systems globally. In this presentation, I will focus on type 2 diabetes (T2D), which accounts for approximately 90-95% of all diabetes cases. T2D is characterized by a progressive decline in insulin secretion often coupled with insulin resistance and metabolic syndrome. While lifestyle factors such as obesity and physical inactivity are well-known contributors, research over the past 25 years has demonstrated that T2D also develops on a genetically predisposed background, as indicated by substantial heritability estimates from family and twin studies (exceeding 40%).
Traditionally, T2D genetics has been viewed through a lens of either monogenic or polygenic causes. However, recent studies have highlighted a more nuanced continuum that includes monogenic, oligogenic, and polygenic factors, each playing a complementary role in T2D pathophysiology. Advances in rare variant research specific to oligogenic T2D are not only enhancing our understanding of disease mechanisms but are also opening avenues for precision medicine that could significantly improve T2D management. To identify these rare oligogenic variants, researchers have employed two main strategies: (i) targeted sequencing of specific candidate genes combined with functional genetic analysis and (ii) comprehensive whole-exome or whole-genome sequencing to uncover low-frequency variants associated with increased T2D risk.
In my presentation, I will explore several key genes implicated in oligogenic T2D, illustrating how these findings deepen our understanding of T2D mechanisms and reveal new potential targets for drug development.

Speaker abstracts

Multi-omic risk factors in ageing populations with a focus on diabetes

Amy Jayne McKnight

School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast

Speaker abstracts

SESSION 3

The interplay between diet, metabolomics, and cardiometabolic diseases: towards precision nutrition

Marta Guasch-Ferré

Associate Professor and Group Leader, Department of Public Health and Novo Nordisk Center for Basic Metabolic Research, University of Copenhagen.

In recent years, advances in high-throughput techniques have enabled the use of metabolomics in epidemiological studies to identify novel biomarkers of disease and elucidate potential biological processes underlying type 2 diabetes and cardiovascular disease etiology. On the other hand, integrating metabolomics into the field of nutrition holds tremendous potential for discovering novel diet-disease biomarkers and identifying key targets for nutritional interventions.

In this talk, I will explore the integration of traditional and omics-based biomarkers, with a particular focus on metabolomics, for disease prevention. I will provide key examples from recent studies that demonstrate the potential of these tools to enhance our understanding of diet-disease interactions. Specifically, I will present findings from an NIH-funded project that I lead as Principal Investigator, titled "Circulating Metabolites, Lifestyle, and Mortality".

I will then introduce the concept of precision nutrition, outlining its definition, goals, and the latest research that aims to tailor dietary interventions based on individual characteristics such as metabolic profiles and genetic predispositions. Drawing on our work, I will present findings related to dietary patterns, lifestyle factors, and their associations with metabolomic profiles and cardiometabolic outcomes.

Finally, I will present unpublished findings from my research group on an emerging topic in the field of nutrition—sustainable diets—and how the integration of sustainable dietary patterns with metabolomics can enhance disease prediction and improve the understanding of the diet-disease associations.

By putting together evidence from the latest scientific literature and my research, this talk will emphasize the potential of precision nutrition in preventing cardiometabolic diseases while also considering the challenges to its implementation. I will conclude with key messages on how these advancements can shape the future of dietary recommendations and public health strategies.

Speaker abstracts

Opportunities and challenges in understanding diabetes pathophysiology in Africa: Insights from T2DM cohorts with low prevalence of common risk factors in Africa

Fredirick Mashili

Exercise Physiology, Physical Activity and Cardiometabolic Health,
Muhimbili University of Health and Allied Sciences (MUHAS), Tanzania

Background: Type 2 diabetes mellitus (T2DM) and its complications are a growing public health challenge in Africa. The coexistence of overnutrition and undernutrition, combined with high rates of infectious diseases such as HIV, malaria, and tuberculosis, and the continent's unique ethnic diversity, may contribute to distinct pathophysiological mechanisms underlying T2DM in African populations—mechanisms that remain largely underexplored. This talk draws on observations from a Tanzanian cohort of newly diagnosed T2DM patients and other African T2DM cohorts to highlight opportunities and challenges in understanding diabetes pathophysiology in the region.

Results: In the current analysis, the Tanzanian cohort was subcategorized based on place of birth/origin (Tanzania mainland and Zanzibar). Both groups showed high proportions of lifetime abstainers from cigarette smoking (92% for mainland and 95% for Zanzibar) and alcohol (82.0% and 97.2%), high physical activity levels (62.4% and 64.0%), and a predominance of individuals with normal weight (56% and 52%). The median ages for mainlanders and islanders were 45 and 42 years, respectively. Notably, patients from Zanzibar had a significantly higher proportion with a positive family history of diabetes compared to mainland counterparts (88% vs. 32%). Despite higher abstention rates, individuals from Zanzibar exhibited significantly higher mean fasting glucose levels, poorer glucose control, elevated blood pressure, and increased total body fat compared to those from the mainland.

Discussion: These findings suggest that traditional risk factors, such as smoking and alcohol intake, may not fully explain T2DM pathophysiology in African populations. The observed differences, particularly the higher family history prevalence and adverse metabolic outcomes among the Zanzibar cohort, underscore the possibility of genetic predispositions interacting with environmental factors. Africa's unique health landscape, with a high burden of infectious diseases, coexistence of overnutrition and undernutrition, and broad genetic diversity, suggests that T2DM may follow distinct pathophysiological pathways. The more severe metabolic complications seen among Zanzibar individuals, despite low prevalence of lifestyle risks, highlight the need to further investigate genetic and environmental influences.

Conclusion: The unique profile of T2DM in African populations—where overnutrition and undernutrition coexist, infectious diseases are prevalent, and ethnic diversity is extensive—challenges conventional models of diabetes pathogenesis based on lifestyle risk factors. Addressing diabetes effectively in Africa requires an integrated research approach focused on genetic factors, infection impacts, nutritional transitions, and interactions among these determinants. These insights present challenges but also promising opportunities for research collaborations to uncover the unique mechanisms underlying diabetes in African populations, ultimately informing targeted, culturally relevant interventions to improve health outcomes.

Speaker abstracts

SESSION 4

Auto- and Paracrine sensing of Succinate by SUCNR1/GPR91 as a Metabolic Stress Signal in Adipose, Muscle, Liver and Kidney

Thue W. Schwartz

NNF Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Succinate is a metabolic stress signal for protection and repair - The TCA cycle metabolite succinate accumulates during metabolic stress/hypoxia due to reverse action of succinate dehydrogenase which is an integrated part of the electron transport chain (1,2). Succinate acts as an intracellular regulator but - importantly – is exported by MCTs to serve as an extracellular signal being sensed by SUCNR1 in both auto- and paracrine manners. Thus, besides on metabolically active cells, SUCNR1 is particularly highly expressed by human anti-inflammatory M2-like macrophages, which are even hyperpolarized by succinate/SUCNR1 Gq-signaling (3).
SUCNR1 (GPR91) is molecularly tuned to sense the high local concentrations of succinate – Receptors for peptide hormones, neuropeptides, and monoamines are activated by pico-, nano- and micro-molar agonist concentrations, respectively. In contrast SUCNR1 is activated highly selectively by high micro- to milli-molar concentration of succinate through a mechanism in which two molecules of succinate occupy each of two high-affinity binding sites simultaneously in SUCNR1 (4).
Adipose - in both mouse and man Sucnr1 is highly expressed in adipocytes where succinate inhibits lipolysis through autocrine Gi signaling. However, in mice Sucnr1 is surprisingly not expressed in the myeloid lineage and consequently not involved in paracrine signaling to M2 macrophages (5) as observed in man (3), which complicates interpretations of murine studies.
Muscle - Sucnr1 has been shown to be involved in exercise-induced muscle remodeling (6). However, in muscle the autocrine component is missing as Sucnr1 is not expressed in the actual muscle cells (5, 6). But, in man Sucnr1 is expressed in neighboring M2 macrophages (5).
Liver - Sucnr1 is in mice – as opposed to man - highly expressed in hepatocytes where we find that the receptor is involved in dampening expression of profibrogenic cytokines such as TGFb. In both mouse and man, Sucnr1 is expressed in aSMA positive, activated stellate cells conceivably as part of a paracrine mechanism which in man involves Sucnr1 expressing macrophages/Kupfer cells.
Kidney – In both man and mice Sucnr1 is very highly expressed not in Macula Densa cells as erroneously reported based on misleading antibodies but in the proximal tubules. Proximal tubule cells are metabolically ultra-active and consequently prone to hypoxic stress, which is the key stimulus for succinate accumulation. We therefore propose that SUCNR1 is involved in protection of kidney cells from hypoxic damage, which has been identified as the major driver of e.g. diabetic kidney disease (7).
Conclusion – SUCNR1 sensing of succinate as a metabolic stress signal appears to function at least initially in tissue repair and remodeling in basically all our metabolically active tissues and pharmaceuticals targeting SUCNR1 could potentially be used to protect against/treat diseases such as MASH and diabetic kidney diseases.

1. Winther S et al. Cell Metabol. (2021). 33, 1276–1278.
2. Murphy MP and Chouchani ET. Nat Chem Biol. (2022) 18: 461-469.
3. Trauelsen M et al. Cell Reports (2021) 35: 109246.
4. Shenol A et al.. Mol Cell. (2024)84: 955-966.e4.
5. Abdelmoez AM et al. Am J Physiol Endocrinol Metab. (2023) 324: E289-E298
6. Reddy A et al. Cell (2020) 183: 62-75.e17.
7. Rodriguez-Rodriguez, R. et al. Kidney International Reports (2024) 9: 1419-1428.

Speaker abstracts

Amino acid and sphingolipid metabolism in co-morbidities of diabetes

Christian Metallo

Molecular and Cell Biological Laboratory, Daniel and Martina Lewis Chair, Salk Institute for Biological Studies, La Jolla, CA, USA

Metabolism is central to virtually all cellular functions and contributes to diseases like cancer, metabolic syndrome, and neuropathy. My laboratory applies stable isotope tracers, mass spectrometry, and metabolic flux analysis (MFA) to quantify metabolism in cells, animal models, and human patients. We are particularly interested in understanding how amino acid and lipid metabolism are coordinated in the context of cancer and diabetes. Serine, glycine and one carbon metabolism are critically important for cell function and health, and modulating these nutrients can slow tumor progression. However, these amino acids are also commonly reduced in patients with metabolic syndrome. Here I will detail how we apply MFA and related methods to decipher 1) why serine and glycine are reduced in mouse models of diabetes and 2) how these metabolic changes influence co-morbidities of diabetes. These changes alter sphingolipid metabolism in ways that mimic hereditary sensory neuropathy and macular disease in patients. Along these lines, we have observed that restricting dietary serine and glycine promotes thermal hypoalgesia in C57BL/6 mice. In turn, supplementation of serine or inhibition of sphingolipid biosynthesis both improve sensory function in diabetic mice, suggesting potential therapeutic strategies for treating patients with serine-associated neuropathy. We also provide evidence that fatty acyl-CoA diversity in sphingolipid biosynthesis impacts hepatic steatosis, lipoprotein secretion, and atherosclerosis in low-density lipoprotein receptor (Ldlr)-deficient mice. Collectively, these data provide mechanistic insights into the roles of SPT flux, amino acid metabolism, and fatty acid diversity in driving co-morbidities of diabetes.

Poster abstracts

Presenter name	Poster nr
Buttò, Lorenzo	P6
Byvald, Fabian	P1
Echeverry, Santiago	P3
Garcia Irigoyen, Oihane	P12
Keysendal, Emmy	P7
Kiriako, Georges	P5
Lampousi, Anna-Maria	P8
Miguens Gomez, Alba	P4
Sánchez-Ceinos, Julia	P10
Stenlid, Rasmus	P11
Stone, Virginia	P2
Wei, Yuxia	P9

There are 12 posters to be presented in the foyer/hallway area by the main entrance to Biomedicum.

Poster screens are 145 cm high and 115 cm wide. Materials to attach with will be available.

Presenters of posters with odd numbers will be at their posters 16.15-16.45

Presenters of posters with even numbers will be at their posters 16.45-17.15

Posters to be mounted latest during lunch break.

Poster abstracts

P1 Fabian Byvald

Longitudinal blood microsampling and proteome monitoring uncover early disease markers and facilitate intervention in experimental type 1 diabetes

Anirudra Parajuli[1,#], Annika Bendes[2,#], Fabian Byvald[1] , Virginia M. Stone[1], Emma E. Ringqvist[1], Marta Butrym[1], Emmanouil Angelis[3], Sophie Kipper[1], Stefan Bauer[3], Niclas Roxhed[4,5], Jochen M. Schwenk[2,#], Malin Flodström-Tullberg[1, #]

1. *Department of Medicine Huddinge, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden*
2. *Science for Life Laboratory and KTH Royal Institute of Technology, Solna, Sweden*
3. *Technische Universität München, Germany*
4. *Department of Intelligent Systems, KTH Royal Institute of Technology, Stockholm, Sweden*
5. *MedTechLabs, Karolinska University Hospital, Solna, Sweden*

Background
The etiology and pathogenesis of immune-mediated diseases (IMIDs), including type 1 diabetes (T1D), multiple sclerosis, and rheumatoid arthritis, remain poorly understood. By the time symptoms appear, irreversible tissue damage has already occurred. Therefore, interventions must be applied during the non-symptomatic stage cementing the necessity to identify early disease predictive biomarkers. Current approaches for identifying such biomarkers rely on blood sampling via venipuncture during healthcare visits, limiting our ability to capture rapid and transient fluctuations in diagnostic biomarkers.
Aims
To experimentally test the hypothesis that at-home blood microsampling through finger-pricking and the collection of dried blood spots allows for frequent sampling intervals, thereby facilitating biomarker discovery and early disease interception.
Methods
Small blood samples (5 µl) were collected almost daily from a mouse model for 14 days after infection with a T1D-associated virus, using a method that mimics finger-pricking. The blood samples were transferred to volumetric devices, allowed to dry, and analyzed using proximity extension assays technology.
Results
The approach described here enabled the detection of transiently altered proteins in virus-infected animals, a finding that would have been missed with less frequent sampling. Leveraging this data and machine learning techniques, a classifier predicted with high accuracy (over 90%) whether an animal was infected after day 2 post infection. Treating infected animals with immune serum on days 2 and 3 post infection prevented diabetes development.
Conclusions
This study demonstrates that longitudinal blood microsampling holds promise for pre-symptomatic disease monitoring in humans, aiding biomarker discovery and timely intervention. Integrating genetic risk scores with measurements of autoantibodies or other markers with a proteome-informed intervention strategy could significantly facilitate the prevention of IMIDs, including T1D.

Poster abstracts

P2 Virginia Stone

Human stem cell-derived islets express Coxsackievirus entry receptors and are suitable for studying the effects of infection on human beta cell function and survival

Marta Butrym[1], Emma E. Ringqvist[1], Fabian Byvald[1], Svitlana Vasylovska[2], Virginia M. Stone[1], Varpu Marjomäki[3], Joey Lau[2], Malin Flodström-Tullberg[1*]

[1] *Department of Medicine Huddinge, Karolinska Institutet, Sweden*
[2] *Department of Medical Cell Biology, Uppsala University, Sweden*
[3] *Department of Biological and Environmental Science, University of Jyväskylä, Finland*

Background
Enteroviruses, including Coxsackie B viruses (CVBs), are linked with the development of islet autoimmunity and type 1 diabetes (T1D). Numerous studies detected enteroviruses in islets of individuals with recent or long-duration T1D. Human islets and beta cells are susceptible to enterovirus infections (including CVBs) *in vitro*, resulting in functional impairments and cell death.
Stem cell-derived islets (SC-islets) closely resemble primary human islets and contain various endocrine cell types, including alpha and beta cells. Moreover SC-islets are a more accessible source than primary human islets.

Aims
To examine if SC-islets are a suitable model for studying CVB infection of human islet cells.

Methods
Surface expression of CVB receptors and hormone expression in dissociated SC-islets was measured by flow cytometry. SC-islets were infected with CVBs and mock-treated or treated with interferons or antiviral drugs (Vemurafenib and its analogue PLX7904). Replicating virus was measured by plaque assay.

Results
Eight separate batches of SC-islets were dissociated into single cells and stained for CAR and DAF/CD55 surface expression. In most batches, the majority of cells were DAF positive (80% to 98%), with 25% to 55% CAR positive. Insulin-positive (beta) cells predominantly expressed CAR, while glucagon-positive (alpha) cells were DAF positive and often co-expressed CAR. CVB3 replicated in all SC-islet batches. Higher multiplicity of infections (MOIs) resulted in higher titres of replicating virus in the supernatant compared to infection with lower MOIs, in a similar dose-range to primary human islets. Importantly, treatment with interferon, Vemurafenib, and PLX7904 provided protection against CVB3 infection.

Conclusions
The robust expression of CAR in insulin-positive SC-islet cells along with their susceptibility to CVB infection highlights their value as a model for investigating the impact of CVB infections on human beta cell antiviral defence mechanisms, function, and survival. Additionally, SC-islets may serve as a useful platform for evaluating novel antiviral therapies.

Poster abstracts

P3 Santiago Echeverry

STOICHIOMETRY AND LOCATION OF PROTEINS AT THE INSULIN GRANULE EXOCYTOSIS SITE.

Santiago Echeverry, Jan Saras, and Sebastian Barg.

Uppsala University, Department of Medical Cell Biology (MCB), Barg's Lab. Uppsala, Sweden.
santiago.echeverry@mcb.uu.se

Pancreatic β-cells control glucose metabolism by insulin, which is released by regulated exocytosis of secretory granules. Preparation of these granules for exocytosis involves recruitment of numerous proteins to the release site, including the core SNARE protein fusion machinery, regulatory SNARE-binding proteins, and structural proteins similar to those of the neuronal active zone. Quantitative information about these proteins' stoichiometry, organization and mobilization at the release site is lacking. Here we used TIRF- and single-molecule microscopy to quantify the copy number and location of SNARE proteins, accessory-, and scaffold proteins at individual insulin granule release sites of live cells. Copy number was estimated by calibrating the fluorescence intensity of EGFP-tagged proteins at the release site with the intensity of single EGFP molecules. Location, and diffusion coefficient relative to the release site were obtained by stochastic superresolution imaging (PALM) and Single Molecule diffusion maps (SMDM), combined with massive averaging in vivo. We estimate that a release site carries on average 20 to 45 copies of syntaxin1, VAMP2, munc18-1, RIM1/2, and ELKS well in excess of estimates of the number of SNARE complexes formed during exocytosis. Ca^{2+}-dependent proteins that act during granule priming, munc13-1 and CAPS, were found at the release site in 3 to 5-fold lower copy number than SNARE proteins. The structural proteins Liprinα1-4 clustered in the plasma membrane in zones with local high granule density despite showing few molecules at the granules release site. SNARE proteins directly involved in the fusion reaction have a density half-peak within 80-90 nm from the center of the granule center, Munc13's distribution half-peak was within 103 +- 11 nm followed by the structural proteins RIM2, ELKS and Lirpina-4 located within 120-156 nm. SMDM of the proteins showed a significant decrease in the diffusion coefficient near the granule center for syntaxin-1, munc18-1, Munc13-1, and RIM2. The study demonstrates that super-resolved imaging, combined with quantitative image analysis and signal processing, derives stoichiometries and protein localizations that may constrain the molecular model of insulin exocytosis and membrane polarization.

Keywords: Insulin Exocytosis, Protein Stoichiometry & Photo Activable Microscopy.

Poster abstracts

P4 Alba Miguéns-Gómez

GLP-1R TRAFFICKING AND SIGNALLING IN β-CELLS

Alba Miguéns-Gómez, Sebastian Barg

Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden

It is well known that many G protein-coupled receptors (GPCRs) aggregate on specific membrane regions before being internalised. Different agonists such as GLP-1 or exendin-4 can trigger glucagon-like peptide-1 receptor (GLP-1R) clustering. However, the specific role of these clusters remains unclear.

Activated GLP-1R triggers intracellular signalling via adenylyl cyclase, while receptor desensitization occurs through β-arrestin binding and receptor internalization, limiting further activation. Recent evidence suggests that GLP-1R signals both from the plasma membrane and from endosomes.
This receptor undergoes clathrin-mediated endocytosis. There are two different structures: small, round clathrin-coated pits (endocytic spots) and larger, flat plaques (endocytically inactive). Utilizing single-molecule and high-resolution microscopy, we aimed to follow the activated GLP-1R trafficking to elucidate its behaviour and signalling.

Our findings show that upon activation, GLP-1R is recruited to clathrin-coated pits prior to internalization. In INS-1 cells, β-arrestins co-localize with clathrin at the membrane both before and after receptor activation. Receptor activation induces rapid cyclic AMP (cAMP) production and the recruitment of mini-Gαs, confirming receptor activation. Notably, Gαs proteins do not co-localize with GLP-1R clusters in clathrin-coated structures under exendin stimulation.

This suggests that GLP-1R clustering may play a role in receptor desensitization by arrestin interaction and subsequent sequestering of the receptor from the membrane.

Poster abstracts

P5 Georges Kiriako

Mapping and targeting insulin nanoclusters for targeted insulin therapies

Georges Kiriako[1], Tade Idowu[1], Enya Engström[1], José Dias[1,2], Margareta Porsmyr-Palmertz[1], Ana Teixeira[1]

[1]*Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm*
[2]*Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm*

Insulin receptors (IRs) form nanoclusters at the cell membrane, as shown by us and others using super-resolution microscopy. The nanocluster organization of IRs enables multivalent insulin binding using engineered insulin nanoclusters. We developed insulin-DNA origami nanostructures that allow for precise control of the number and spacing of insulin molecules per insulin nanocluster. We found that certain multivalent insulin configurations significantly increased IR activation, extended receptor engagement, and improved glucose regulation in a zebrafish model of diabetes. These results suggest that tuning insulin valency and spatial organization in insulin nanoclusters could open new pathways to improve insulin therapies. Our current studies explore the spatial organization of IRs in key tissues and examine differences in IR clustering between normal and insulin-resistant states. Future work includes investigating the biodistribution and bioactivity of insulin nanoclusters in zebrafish and mouse diabetes models using imaging and single cell sequencing. Understanding tissue-specific IR patterns may allow us to develop new types of insulin nanocluster-based therapies that can selectively target key tissues to fine-tune insulin efficacy at the cellular level.

Poster abstracts

P6 Lorenzo Buttò

Transcriptomics-guided exploration of the zebrafish enteroendocrine system and its response to metabolic and pharmacological stimuli

Lorenzo Buttò[1,2], Jiarui Mi[1,3], Lianhe Chu[1], Anna Johansson[4], Stefan Ebmeyer[5], Agnese Kocere[2], Olov Andersson[1,2]

1. Department of Cell and Molecular Biology, Karolinska Institutet, Sweden
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The enteroendocrine system is known to be a key regulator of metabolic homeostasis in response to a wide spectrum of challenges, but its dynamics is yet to be fully understood. Here we present a transcriptomics-driven analysis of the enteroendocrine cells' activity in the presence of metabolic and pharmacological challenges. We generated a single cell-RNA sequencing dataset from zebrafish subjected to feeding, fasting and diabetes (by targeted beta-cell ablation). We were able to retrieve most of the known hormone signatures in our cell clusters, allowing us to start analyzing the plasticity of such cells across the different conditions. The mentioned dataset also includes three clusters of cells expressing stem cell-related genes; one of these clusters is selectively expresses the Notch ligand *dld*, which we via lineage tracing experiments confirmed to be expressed by secretory progenitors in the zebrafish intestine. Finally, we highlight the possibility to manipulate such secretory progenitors pool using pharmacological treatment, which was able to increase the number of progenitor cells and their lineage-traced hormone-producing descendants. These results provide new insights about the enteroendocrine cells' ability to respond to a spectrum of interventions, reinforcing their role as a druggable target for diabetes.

Poster abstracts

P7 Emmy Keysendal

SMOKING AND THE RISK OF TYPE 2 DIABETES SUBTYPES

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Objective: Recent data-driven cluster analysis has identified four distinct subtypes of type 2 diabetes (T2D), two severe (SIRD-severe insulin resistant, SIDD-severe insulin deficient and two mild (MOD-mild obesity related and MARD-mild obesity related. Genetic differences have been observed between these clusters, but it is not known if environmental risk factors differ. Smoking is associated with an increased risk of T2D. We investigated whether this association varied by T2D subtype.
Methods: We used data from the Swedish case-control study ESTRID (2010-2023) and the Norwegian cohort study HUNT (HUNT1-3, 1984-2008), in total covering 2830 controls, and 843,631 person-years of follow-up together with 3179 incident T2D cases (1124 SIDD, 776 SIRD, 1577 MARD, 673 MOD). We used conditional logistic and Cox regression to estimate odds ratios (OR) and hazard ratios (HR), which were pooled to yield relative risks (RR) with 95% confidence intervals (CI).
Results: Ever vs. never smokers were at increased risk of SIRD (RR_{pooled} 1.53 [95% CI 1.17-1.98]), while the association with smoking was weak for SIDD (RR_{pooled} 1.08 [95% CI 0.87-1.32]), MARD (1.15 [95% CI 1.02-1.30]) and MOD (1.14 [95% CI 0.93-1.39]). For heavy smokers (≥15 pack-years or >20 cigarettes per day vs. never smoking or non-smoking) we observed an increased risk of all four subtypes, but the association appeared stronger for SIRD (RR_{pooled} 1.85 [95% CI 1.36-2.50]) than for SIDD (RR_{pooled} 1.36 [95% CI 1.06-1.75]), MARD (1.28 [95% CI 1.10-1.50]) and MOD (1.54 [95% CI 1.08-2.19]) (Table 1).
Conclusions: Our results indicate that long term heavy smoking promotes T2D whether it is characterized by insulin resistance, insulin deficiency, obesity or high age which highlights the important role of smoking cessation in the prevention of T2D. However, the associations appeared stronger for the subtype characterized by higher insulin resistance. This finding supports that the link between smoking and T2D involves adverse effects on insulin sensitivity. In further analyses, we will explore the association with snus use, as well as the potential interaction with genetic susceptibility to T2D, insulin resistance and insulin secretion estimated by polygenetic risk scores.

Table 1: Pooled relative risks with 95% CIs for type 2 diabetes subtypes in relation to smoking.

			SIDD		SIRD		MOD		MARD	
Smoking	Controls	Person-years	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Never	1428	867,867	205	1	157	1	298	1	634	1
Former	854	643,729	158	1.03 (0.81-1.31)	207	1.41 (1.06-1.88)	174	0.97 (0.76-1.24)	639	1.20 (1.05-1.38)
Current	526	444,396	115	1.12 (0.86-1.45)	87	1.76 (1.23-2.51)	201	1.32 (1.04-1.68)	304	1.09 (0.92-1.28)
Ever	1380	1087,125	273	1.08 (0.87-1.32)	294	1.53 (1.17-1.98)	375	1.14 (0.93-1.39)	943	1.15 (1.02-1.30)
Intensity (current)										
Non-smoking	2282	867,867	324	1	349	1	404	1	1038	1
<20 cig/day	392	429,723	101	1.00 (0.72-1.39)	75	1.58 (1.10-2.26)	188	1.25 (0.99-1.58)	365	1.11 (0.95-1.28)
≥20 cig/day	86	176,476	34	0.97 (0.78-1.20)	19	1.43 (0.76-2.69)	62	1.54 (1.08-2.19)	93	1.18 (0.92-1.52)
per 5 cigarettes	478	917,706	135	1.08 (1.00-1.17)	94	1.16 (1.04-1.29)	250	1.11 (1.03-1.19)	458	1.02 (0.97-1.07)
Pack-years (ever)										
Never	1432	867,867	205	1	157	1	300	1	634	1
<15 pack-years	692	562,174	106	0.93 (0.71-1.21)	93	1.28 (0.92-1.80)	199	1.13 (0.89-1.42)	381	1.12 (0.96-1.31)
≥15 pack-years	606	349,541	146	1.36 (1.06-1.75)	184	1.85 (1.36-2.50)	149	1.20 (0.91-1.58)	458	1.28 (1.10-1.50)
Per 5 pack-years	1298	910,715	252	1.01 (1.00-1.02)	277	1.02 (1.00-1.04)	348	1.01 (0.99-1.03)	839	1.00 (0.99-1.01)

Adjusted for age, sex, BMI, education, and alcohol consumption. Controls derived from ESTRID. Person-years derived from HUNT.

Poster abstracts

P8 Anna-Maria Lampousi

Alcohol consumption, genetic susceptibility to diabetes, and risk of LADA and type 2 diabetes: findings from a Swedish case-control study and the Norwegian HUNT study

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Background: Alcohol consumption has been inversely associated with type 2 diabetes (T2D), but its influence on autoimmune diabetes is unclear. We investigated the risk of latent autoimmune diabetes in adults (LADA) and T2D in relation to alcohol intake and assessed if potential associations were modified by genetic susceptibility to diabetes.

Methods: We used data from a Swedish case-control study with incident diabetes cases (n=695 LADA and n=2,679 T2D) and matched controls (n=2,752), and the Norwegian prospective study HUNT with 1,097,026 person-years of follow-up and incident diabetes cases (n=221 LADA and n=3,335 T2D). Pooled relative risks (RR) with 95% confidence intervals (CI) were estimated in relation to self-reported alcohol consumption. Analyses were stratified according to HLA risk genotypes and polygenic score (PGS) for T2D (T2D-PGS)

Results: Moderate alcohol consumption (10-14.9 g/day) compared to low consumption (0.1-4.9 g/day) was associated with a reduced risk of LADA (RR: 0.74, CI: 0.56, 0.98) and T2D (RR: 0.81, CI: 0.69, 0.94). Similar RRs were observed for the highest intake category (≥15 g/day). Stratification by T2D-PGS revealed an inverse association with LADA in those with high T2D-PGS (≥10 g/day vs. 0.1-4.9 g/day; RR: 0.45, CI: 0.26, 0.78), but not low/intermediate T2D-PGS (RR: 0.89, CI: 0.51, 1.53). The corresponding RRs for high- and low/intermediate-risk HLA carriers were 0.64 (CI: 0.35, 1.17) and 0.48 (CI: 0.31, 0.74). For T2D, inverse associations with alcohol were evident in those with low/intermediate T2D-PGS (RR: 0.71, CI: 0.53, 0.93) but not high T2D-PGS (RR: 0.85, CI: 0.62, 1.16).

Conclusions: Moderate alcohol intake was linked to reduced LADA risk, particularly in individuals with high T2D-PGS and low/intermediate-risk HLA-genotypes, indicating that the association is primarily present for T2D-like LADA. Conversely, the inverse association between alcohol and T2D may apply mainly to those without genetic predisposition.

Poster abstracts

P9 Yuxia Wei

Stable Heritability of Type 1 Diabetes: Results from a Genetically Informed Cohort Study

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Background: Incidence of type 1 diabetes is increasing globally, which has been attributed to environmental influences. It is unknown if this has made type 1 diabetes a less heritable disease.

Objective: To investigate if the relative contribution of genetic and environmental influences on childhood-onset type 1 diabetes etiology has changed over time and how alterations in environmental factors have contributed to rising type 1 diabetes incidence in Sweden.

Design: Population-based nationwide cohort study.

Setting: Sweden.

Participants: All children (n=2,928,704, including 1,549,357 full sibling pairs) born 1982-2010. They were linked to their parents and siblings and followed until 2020.

Measurements: Information on environmental factors and type 1 diabetes was retrieved from nationwide registers.

Results: Type 1 diabetes incidence increased from birth year 1982 (cumulative incidence 0·50%) to 2000 (0·93%) and remained stable thereafter. The heritability was estimated at 0·83 (95% confidence interval [CI]: 0·79, 0·86) overall, and stable over the observation period (0·80 [95% CI: 0·71, 0·86] in 1982, 0·83 [95% CI: 0·79, 0·86] in 2000, and 0·83 [95% CI: 0·79, 0·86] in 2010, respectively). Environmental factors including maternal smoking during pregnancy and childhood adiposity explained <10% of the increasing type 1 diabetes incidence.

Conclusions: Heritability of type 1 diabetes has remained high and stable over the last 30 years. The contribution of environmental factors to type 1 diabetes does not increase over time.

Poster abstracts

P10 Julia Sánchez-Ceinos

The circulating environment of adolescents exposed to gestational diabetes *in utero* induces endothelial dysfunction via oxidative stress

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Gestational diabetes (GD) is a common pregnancy complication. Beyond its well-known perinatal effects, like macrosomia, children born to women with GD face a higher risk of developing atherosclerotic cardiovascular disease (ASCVD) later in life through yet unknown mechanisms. Based on our previous observations, we hypothesize that an abnormal circulating environment in GD-offspring may alter their vascular function, elevating their ASCVD risk. To test this, plasma samples from healthy adolescents born to either normoglycemic women (control, n=8) or women with GD (GD, n=12) were collected. Then, vascular function of mouse aortas incubated with adolescent´s plasma was assessed by myograph.

Aortas incubated with control-plasma exhibited robust endothelium-dependent relaxations (EDR), whereas those exposed to GD-plasma showed significantly reduced EDR, indicating endothelial dysfunction. In contrast, endothelium-independent relaxations remained unchanged among experimental conditions. To explore the processes behind this endothelial damage, we examined different markers in human aortic endothelial cells (HAECs) treated with the same plasma samples. RT-PCR studies revealed that cells exposed to GD-plasma had increased mRNA content of *NF-kB*, *ICAM1*, and *IL18* compared to controls. Moreover, these cells also displayed elevated transcript levels of nearly all the anti- and pro-oxidant genes tested (*CAT*, *GPX1*, *PRDX1*, *SOD1, SOD2*; and *NOX4*, *COX1*, *COX2*, respectively), suggesting that GD-plasma promotes inflammation and, more pronouncedly, oxidative stress in endothelial cells. Moreover, the GD plasma-induced poor EDR was reversed by antioxidant agents, confirming oxidative stress as a key driver in this setting. Finally, correlation analysis showed significant associations between EDR and gene expression results with macrosomia-related features at birth, but not with obesity at adolescence.

Taken together, our results suggest that adolescents exposed to GD *in utero* have an aberrant circulating environment that may compromise endothelial function via oxidative stress, contributing to ASCVD risk. These findings could guide early preventive strategies to mitigate cardiovascular complications in this vulnerable population.

Poster abstracts

P11 Rasmus Stenlid

The MINT-study: A randomized controlled trial of metformin treatment for children and adolescents with obesity

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Aims: Lifestyle interventions form the basis of treatment for pediatric obesity, but have shown limited success and thus pharmacotherapy is often needed. The GLP-1 agonists liraglutide and semaglutide are indicated for both type 2 diabetes and obesity from the age of twelve. Metformin is indicated for type 2 diabetes from the age of ten, but not indicated for pediatric obesity. Results from clinical trials of metformin in children with obesity have been ambiguous, with outcomes varying depending on dosage and age. Metformin extended release (XR) has shown promising results in adults. This trial investigated the change from baseline in BMI-SDS for Metformin XR in combination with lifestyle intervention, compared with lifestyle intervention alone.
Methods: A parallel, three-armed (metformin XR and lifestyle, metformin immediate release (IR) and lifestyle, or lifestyle alone), randomized, 6-month study in children and adolescents, aged 6-18 years, with obesity (BMI-SDS >2.0). Subjects randomized to drug treatment received weight-adjusted doses of metformin. Lifestyle treatment was given to all participants. The primary endpoint was analyzed by Analysis of Covariance.
Results: There were 89 subjects randomized, and 77 subjects completed the study. Reduction in BMI-SDS was greater in the Metformin XR group, compared with lifestyle intervention alone (difference between groups 0.128 SD, p=0.03). Mean BMI-SDS change from baseline to the end of the study was -0.280 (p=0.009) for the Metformin IR group, -0.281 (p=0.006) for the Metformin XR group, and -0,126 (p=0.359) for lifestyle intervention alone. There were no significant changes in other metabolic parameters between baseline and end of study in any of the groups, besides a reduction in 2-hour insulin in the Metformin IR group.
Conclusion: Both Metformin IR and Metformin XR in combination with lifestyle modification interventions lower BMI-SDS and could be suitable options for the treatment of pediatric obesity.

Poster abstracts

P12 Oihane Garcia-Irigoyen

Hepatocyte-specific depletion of the corepressor GPS2 alleviates atherosclerosis and dyslipidemia in mice

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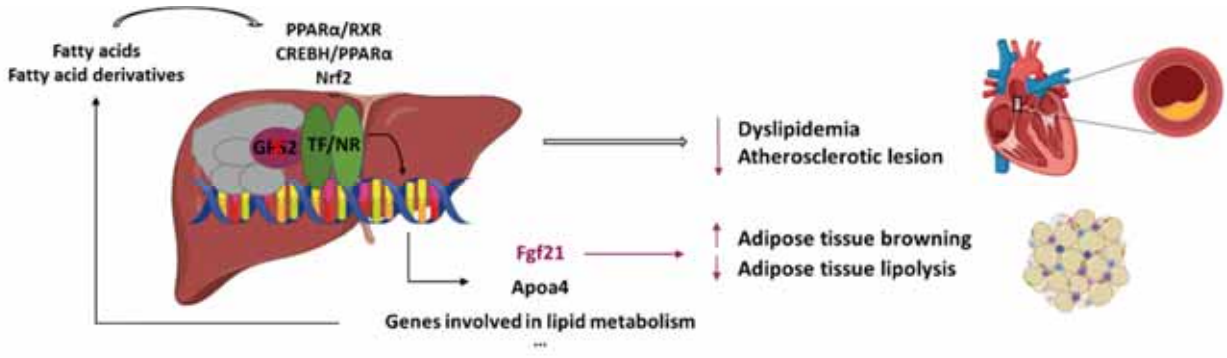
Alterations of hepatic lipid metabolism and liver disorders have been implicated in the pathogenesis of atherosclerosis, a chronic cardiovascular inflammatory disease. Metabolic dysfunction-associated fatty liver disease, for instance, has been linked with insulin resistance, obesity, and metabolic syndrome, conditions known to be associated with cardiovascular disease and subclinical atherosclerosis. Our previous work has demonstrated that hepatocyte-specific GPS2 knockout in mice alleviates diet-induced steatosis and fibrosis and causes activation of lipid catabolic genes by de-repression of PPARα.

To analyse how liver GPS2 pathway affects atherogenesis, we have generated hepatocyte-specific GPS2 KO mice in the ApoE KO background (ApoE-LKO).

ApoE-LKO mice showed smaller atherosclerotic lesion areas in the aortic root, their body and epididymal fat pad weights were lower, exhibited less atherogenic lipoprotein profiles, and their liver cholesterol content was decreased along with an increase in bile cholesterol secretion. In addition, the hepatic expression of inflammatory genes was reduced, together with changes in lipid metabolism gene expression. The expression of fibroblast growth factor 21 (FGF21) was increased in liver, as well as circulating FGF21 levels. Furthermore, we demonstrate that liver-specific FGF21 knockdown using AAV-shRNA seems to corroborate the atheroprotective effect of FGF21 induction in ApoE-LKO mice, but it cannot explain completely the athero-protective phenotype.

Collectively, our study suggests that the loss of the corepressor GPS2 in hepatocytes improves atherosclerosis development and alleviates dyslipidemia. We propose that this phenotype is in part caused by the induction of FGF21, but also by the generation of fatty acids and derivatives that likely act as signalling molecules (e.g. to modulate activity of transcription factors including nuclear receptors). Mechanistically, the loss of GPS2 directly causes chromatin remodelling at cis-regulatory elements of regulated genes to de-repress transcription. Which transcription factors (in addition to PPARs) are the direct targets for GPS2 in hepatocytes remains to be clarified.



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