8th EGID SYMPOSIUM

"*Latest insights in diabetes research*"

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Book
Programme & Abstracts

Content

November 12th, 2025 - Lille Grand Palais

E.g.i.d.
European Genomic Institute for Diabetes

8th EGID SYMPOSIUM

"*Latest Insights in Diabetes Research*"

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November 12, 2025 - Lille Grand Palais

THE 8th EGID SYMPOSIUM
LATEST INSIGHTS IN DIABETES RESEARCH

08.30	Registration
09.00	Welcoming & Introduction
09.10	Pr. Reiner JUMPERTZ-VON SCHWARTZENBERG, Tübingen - GERMANY Prediabetes Remission: A new Concept for Improving Diabetes Prevention
09.50	Pr. David RAY, Oxford - UK Emerging Links Between the Sleep and Circadian System and Cardiometabolic Disease
10.30	Coffee Break
10.50	Pr. Torben HANSEN, Copenhagen - DENMARK Uncovering Genetic and Molecular Drivers of Insulin Secretion and Diabetes: From Arctic Populations to Early Childhood
11.30	Pr. Lorenzo PIEMONTI, Milan - ITALY Rethinking Beta Cell Transplantation : Questions and Frontiers
12.10	Lunch
13.10	Posters Session
14.40	Pr. Fabiana PEROCCHI, Munich - GERMANY Systematic Reconstruction of Mitochondrial Calcium Signaling Networks in Health and Disease
15.20	Pr. Heiko LICKERT, Munich - GERMANY Inceptor – a Novel Regulator of Insulin Signaling and Beta Cell Biology
16.00	Coffee Break
16.20	Legacy & Perspective
16.50	Best Poster Award and Conclusions
17.00	Thanks and Refreshments

Speakers Abstracts

David RAY,
Professor of Endocrinology, and Head of Oxford Centre for Diabetes, Endocrinology, and Metabolism
Governing body fellow, Wolfson College, Oxford
Sir Jules Thorn Sleep and Circadian Neuroscience Institute (SCNi)
Oxford Kavli Centre for Nanoscience Discovery, University of Oxford

> Emerging links between the sleep and circadian system and cardiometabolic disease

In the UK more than 4.3 million people live with Type-2 Diabetes (T2D), and 2.4 million more are at increased risk of developing the disease. T2D, obesity, hypertension, and fatty liver disease frequently cluster together in the same individuals, termed cardiometabolic multimorbidity. The risk factors for cardiometabolic disease (CMD) are multiple, but disturbances sleep and circadian rhythm disruption (SCRD) is emerging as an important driver of disease incidence and severity. But importantly, SCRD is also promoted by CMD; thereby creating a vicious cycle perpetuating poor health and wellbeing.

Here, we employ a genetic co-localisation approach in the UK Biobank to find loci that associate with both a SCRD, and a CMD phenotype, or trait. This approach was designed to identify the shared genetic architecture between the two interrelated systems : CMD, and SCRD. This identified a number of loci with varying confidence intervals and estimated statistical significance. One locus attracted attention due to its high statistical significance and tightly defined genetic interval around a single genetic variant (rs12140153).

The putative causal SNP (rs12140153) is a missense variant within PATJ, a gene encoding a membrane-bound protein associated with tight junctions. PATJ has been identified in previous GWAS studies of body mass index (BMI) and with C-reactive protein (CRP; marker of systemic inflammation), and widespread expression in human tissues (with protein levels highest in brain (cerebellum), GI tract, muscle and immune related tissues). We further analysed a different, cardiometabolic-focussed biobank in Oxford, UK and identified significant numbers of people with rare, deleterious coding region variants. These individuals had significant changes in serum lipid concentrations, especially affecting sphingolipids. Sphingolipids are implicated in cardiometabolic disease, and cellular sphingolipid metabolism is associated with changes in circadian function.
In summary, large human cohort analysis has the potential to identify new genetic drivers of SCRD and CMD.

Fabiana PEROCCHI

Associate Professor of Systems Biology of Metabolism at the Technical University of Munich (TUM); Head of Research Unit in Functional Genomics of Mitochondria at the Helmholtz Diabetes Center and Institute for Diabetes and Obesity ofg the Helmholtz Munich

> Systematic reconstruction of mitochondrial calcium signaling networks in health and disease

Mitochondria function as major intracellular calcium signalling hubs, able to sense, decode, and respond to cytosolic calcium transients thanks to the coordinated activity of calcium uptake and efflux pathways. Although mitochondrial calcium handling and its biophysical properties have been documented over 60 years ago, the genetic identity of the underlying machineries started to unravel only in the past two decades. Discoveries of members of the mitochondrial calcium uniporter channel (MCUC) have been propelled by the development and application of top-down computational and experimental approaches that leveraged machine learning-based prediction of mitochondrial protein localization, whole-genome-sequence-based evolutionary analyses, protein-protein interaction mapping, and genome-wide loss-of-function screens. Those findings have finally opened the doors for targeted genetic manipulations and demonstrated that mitochondrial calcium deregulation is a hallmark of rare and common pathologies. Furthermore, MCUC is part of a broader functional network and can respond to changes in local cellular environment through dynamic protein-protein interactions with other mitochondrial complexes and pathways, involved in ATP production, cristae morphology, and proteostasis. Therefore, **the pleiotropic role of mitochondrial calcium homeostasis reflects great diversity in the molecular composition and regulation of calcium signalling machineries, pathways and networks across different organs and cell types**. However, little is known on how MCUC-mediated signalling remodel during disease, such as for example diet-induced nonalcoholic fatty liver (NAFLD). **This presentation will showcase how systems' level approaches can help disentangling such a complexity.**

Heiko LICKERT

Director of the Institute of Diabetes & Regeneration Research, Helmholtz Munich

> Inceptor – a novel regulator of insulin signaling and beta cell biology

Resistance to insulin and insulin-like growth factor 1 (IGF1) in pancreatic β-cells causes overt diabetes in mice; thus, therapies that sensitize β-cells to insulin may protect patients with diabetes against β-cell failure. Previously, we identify an inhibitor of insulin receptor (INSR) and IGF1 receptor (IGF1R) signalling in mouse β-cells, which we named the insulin inhibitory receptor (in short: inceptor). Strikingly, inceptor knock-out in beta cells increased the activation of INSR-IGF1R and increased proliferation of beta cells, resulting in improved glucose tolerance in chow and high-fat diet mouse models. Mechanistically, inceptor interacts with INSR and IGF1R to facilitate clathrin-mediated endocytosis for receptor desensitization. To explore the function of inceptor in a human relevant model, we generated an inceptor knock-out (KO) human induced pluripotent stem cell (iPSC) line and derived iPSC-derived islets. This showed that inceptor KO resulted in increased human SC-β-cell differentiation, survival and function, in line with our previous findings in murine β-cells. Strikingly, we identified proinsulin and insulin as ligands for inceptor. At the plasma membrane, inceptor binds and internalizes insulin for lysosomal degradation via clathrin-coated endocytosis.

Furthermore, we describe a novel intracellular role of inceptor as a trans-Golgi network sorting and lysosomal degradation receptor for proinsulin. Taken together, inceptor is a (pro)insulin degradation receptor and IR/IGF1R desensitizer and as such a very intersting molecular target to replenish insulin stores and β-cell mass and function.

Lorenzo PIEMONTI
Director Diabetes Research Institute Università Vita Salute Milano

> Rethinking Beta Cell Transplantation: Questions and Frontiers

Beta cell transplantation has long held promise as a therapeutic avenue for insulin-dependent diabetes, particularly type 1 diabetes. Despite encouraging advances in clinical outcomes and the refinement of islet and beta cell replacement strategies, several fundamental challenges continue to limit the widespread application of this therapy. These include immune-mediated graft rejection, the need for life-long immunosuppression, limited donor availability, and the lack of durable long-term graft function. In recent years, the field has seen a surge of innovation, from stem cell–derived beta cell products and encapsulation technologies to novel immunomodulatory approaches aiming to induce tolerance or protect grafts without systemic immunosuppression. Yet, the transition from experimental platforms to standardized clinical solutions remains fraught with unanswered questions. This presentation will explore the current state of beta cell replacement therapies, critically assess ongoing clinical and translational efforts, and highlight the scientific and logistical frontiers that must be addressed to move toward scalable, safe, and durable cures. By reframing key questions and embracing emerging interdisciplinary strategies, we can chart a new course for the future of beta cell transplantation.

Reiner JUMPERTZ-VON SCHWARTZENBERG
Head of Clinical Study Center
Institute for Diabetes Research and Metabolic Diseases
Helmholtz Center Munich at University of Tübingen
German Center for Diabetes Research

> Prediabetes remission: A new concept for improving diabetes prevention

More than 1 billion individuals world-wide live with type 2 diabetes (T2D) or prediabetes. However, for more than 20 years, treatment paradigms to prevent T2D have not changed.

In 2018 the Taylor Group demonstrated that T2D can be brought into remission by severely calorie restricted diets and that T2D remission involved improved of beta cell secretory capacity, reductions in liver fat and pancreatic fat, factors which also play a role for T2D relapse mechanisms. Considering the natural history of T2D development, insulin sensitivity first gradually declines until T2D develops when the beta cell cannot compensate the prevailing insulin resistance. Thus, we hypothesized that remission of prediabetes is mainly chaperoned by improvements in insulin sensitivity. To answer this question, we investigated data from the Prediabetes Lifestyle Intervention Study (PLIS), a multicenter study by the German Center for Diabetes Research. This study includes more than 1000 individuals with prediabetes who undergo conventional or intensified lifestyle intervention paradigms for 1 year. We defined remission of prediabetes by normalization of fasting glucose, 2h glucose and HbA1c.

During the prediabetes remission with significant weight loss, indeed insulin sensitivity mainly improves which is associated with reductions in visceral adipose tissue (VAT). Most importantly, remission of prediabetes was associated with a 73 % reduction in future T2D. More recently, we demonstrated that prediabetes remission is even possible without weight loss, that the underlying mechanisms involve reductions in insulin resistance, VAT but also improvements in insulin secretion linked with improved beta cell GLP-1 sensitivity. Surprisingly, also non-weight loss associated remission was associated with a >70% T2D risk reduction. Finally, we could demonstrate that the remission of prediabetes is even associated with reduced cardiovascular endpoints and mortality.

These data highlight the need for a treatment paradigm shift from pure weight loss goals towards combined goals including glycemic targets.

Torben HANSEN

Professor, MD, Ph.D., Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark

> Uncovering Genetic and Molecular Drivers of Insulin Secretion and Diabetes: From Arctic Populations to Early Childhood

How do our genes and proteins shape the risk of diabetes? Professor Torben Hansen explores this question by combining cutting-edge genomic and proteomic research with unique insights from diverse populations. From Greenland, where Arctic adaptation has revealed striking genetic variants, to studies in children that identify early molecular signatures of metabolic health, his work highlights the pathways that govern insulin secretion and diabetes susceptibility.

He will also present THE TRANSLATE PROJECT, a pioneering initiative in precision medicine that uses DNA research to improve diagnosis and treatment of non-autoimmune diabetes. Together, these studies show how diversity and molecular insights can transform the future of diabetes care.

Omaima BINAN

Data-Driven Clinical Clusters of Insulin Resistance Uncover Transcriptomic Signatures in Skeletal Muscle

Omaima Binan[1,2], Lucas Maurin[1,2], Bénédicte Toussaint[1,2], Souhila Amanzougarene[1,2], Mehdi Derhourhi[1,2], Violeta Raverdy[2,3], François Pattou[2,3], Amélie Bonnefond[1,2], Philippe Froguel[1,2,4], Nicolas Gambardella[1,2], Amna Khamis[1,2]

[1]*Inserm UMR1283, Cnrs UMR 8199, France.*
[2]*Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, Egid, F-59000 Lille, France.*
[3]*Inserm, Translational Research in Diabetes (U1190), Lille, France.*
[4]*Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom.*

Scientific context : Insulin resistance is a key metabolic defect in obesity, with skeletal muscle as a primary site of impaired glucose uptake.

Objectives : To better characterize the clinical heterogeneity of insulin resistance by identifying distinct subgroups and their associated transcriptomic signatures in skeletal muscle.

Materials and Methods : We analyzed 84 individuals from the ABOS bariatric surgery cohort, selected to represent a wide range of HOMA2-IR insulin resistance measures. We used K-medoids clustering to identify subgroups using eight key insulin resistance features (age, BMI, HOMA2-IR, HOMA2B, insulinogenic index, fasting insulin, fasting glucose, C-peptide/glucose ratio). The optimal cluster number was determined via the elbow method with Jaccard stability validation. To identify transcriptomics differences between the groups, we performed differential gene analysis from RNA sequencing data generated from muscle tissue from all individuals.

Results and Discussion : This approach identified three clinically distinct subgroups: Cluster 1 (40.4%), composed of metabolically healthy individuals; Cluster 2 (33.3%), with moderate insulin resistance, and Cluster 3 (26.3%), characterized by severe insulin resistance. Clusters showed differences in glycemic indices, insulin levels, and beta-cell function, while lipid profiles remained similar across groups. We performed a transcriptomic analysis, and identified 10 genes significantly associated with the clusters, the analyses took account of multiple tests with the Benjamini–Hochberg adjustment using an FDR < 0.05. Among the top hits were *SOCS3, MTCO2P12* and IL6 previously implicated in insulin sensitivity and inflammation, respectively. Pathway analysis using Metascape identified five enriched pathways related to oxygen transport and oxidative stress response, processes essential for muscle metabolism and insulin sensitivity.

Conclusion and Perspectives : Individuals with obesity can be stratified into distinct insulin resistance subtypes that exhibit distinct muscle transcriptomic signatures, offering novel insights into muscle-specific insulin resistance pathophysiology.

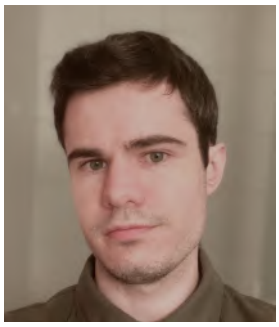
Arthur CENS

Role of FAT10 in Mallory Denk Bodies formation during MASH development in hepatocytes

Arthur Cens[1], Cyril Bourouh[1], Claire Devos[1], Fabienne Glacial[1], Nathalie Hennuyer[1], Lucie Bernard[1], Audrey Helleboid[1], An Verrijken[2], Vivianne Gnemmi[3], Sven Francque[2], François Pattou[4], Guillaume Lassailly[3], Bart Staels[1], Réjane Paumelle[1].

[1]*Université de Lille, INSERM, CHU, Institut Pasteur de Lille, U1011-EGID, France*
[2]*Hôpital universitaire d'Anvers, TWI2N, Edegem, Belgium*
[3]*Hôpital Claude Huriez, Service maladies de l'appareil digestif, France*
[4]*Université de Lille, INSERM, CHU, UMR 1190 – EGID, France*

The Metabolic dysfunction-Associated Steatohepatitis (MASH) is the first step of hepatocyte suffering development in a metabolism trouble context, leading to cirrhosis and hepatocellular carcinoma. Suffering hepatocytes are characterized by ballooning and Mallory-Denk Bodies (MDB) formation, which are protein aggregates composed with p62 and Keratin 8/18 (K8/18). Patients with MDBs are known to have a higher risk of liver relative death. These protein aggregates are induced after an alteration of protein degradation pathways in ballooned hepatocytes. Previously, the ubiquitin like modifier FAT10 has been shown to increase during MASH development, and to be involved in MDB formation in an acute liver injury context other than MASH. Nowadays, there is no study investigating the role of FAT10 in MDBs development during MASH. The transcriptomic analysis of livers of MASH patients with ballooning shows positive correlation between FAT10 and MDB biomarker expression. Liver histology reveals that patients with MDBs in hepatocytes have an increase of FAT10 positives aggregates. Moreover, FAT10 overexpression in hepatocytes is associated to MDBs formation in vivo and in vitro under MASH conditions. Interestingly, FAT10 downregulation in HepG2 cells decreases MDB formation induced by MASH-like conditions by regulating autophagy pathway. In addition, FAT10 deficiency in hepatocytes of MASH mice decreases MDBs formation. Altogether, these results demonstrate that an increase of FAT10 expression during MASH development participates to MDB formation and hepatocyte suffering.



Evan COURMONT

Novel regulators of pathological endothelial-to-mesenchymal transition (EndMT)

Courmont E.[1], Machmouchi A.[1], Bettaieb L.[1], Goveia J.[2], Cantelmo A.R.[1]

[1]*Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-EGID, F-59000 Lille, France, 2Unicle Biomedical Data Science, Leuven, Belgium*

Endothelial-to-mesenchymal transition (EndMT) is a pathological process whereby endothelial cells (ECs) lose their identity and acquire mesenchymal characteristics. This transition contributes to vascular remodelling and disease progression in various cardiovascular conditions, including atherosclerosis and diabetes. Understanding the molecular mechanisms driving EndMT is essential to develop new therapeutic strategies to preserve endothelial function and reduce vascular pathology.

In this project, we aimed to identify novel regulators of EndMT through an integrative bioinformatic and experimental approach. A comprehensive meta-analysis of publicly available transcriptomic datasets including multiple EndMT models and pathological contexts was performed to uncover consistently upregulated genes. This analysis generated a list of genes recurrently associated with EndMT across diverse conditions. Among these, the nuclear receptor Peroxisome proliferator-activated receptor alpha (PPARα), a transcription factor known to play protective roles in lipid metabolism, inflammation, and vascular homeostasis, was highlighted as one of the most consistently upregulated among the athero-associated candidates.

To validate these findings, we established an *in vitro* model mimicking pro-atherogenic conditions, exposing ECs to oxidized low density lipopreotein (LDL) and inflammatory cytokines. To assess whether PPARα modulates EndMT in atherosclerosis conditions, we treated our athero-EndMT model with pemafibrate, a selective PPARα agonist. Western blot analysis confirmed increased PPARα levels associated with partial restoration of endothelial identity (increased expression of the endothelial marker CD31, and reduced expression of the mesenchymal marker Snail), suggesting a partial rescue from EndMT following PPARα activation. Functionally, pemafibrate-treated EndMT cells exhibited improved barrier integrity, as evidenced by decreased permeability.

Together, these results suggest that PPARα activation may attenuate EndMT and help maintain endothelial identity and function in pathological conditions. Thus, PPARα activation may represent a promising therapeutic strategy to limit EndMT-driven vascular remodeling in atherosclerosis.

Keywords:
Endothelial-to-Mesenchymal Transition (EndMT), Atherosclerosis, PPARα (Peroxisome Proliferator-Activated Receptor Alpha), Endothelial Dysfunction, Cardiovascular Disease.

Audrey DEPRINCE

Somatic mosaicism in liver linked to hyperglycemia in metabolic dysfunction-associated steatohepatitis

Audrey Deprince[1], Mehdi Derhourhi[1], Bénédicte Toussaint[1], Souhila Amanzougarene[1], Shuangshuang Geng[1], Frédérik Oger[1], Amna Khamis[1], Emmanuel Vaillant[1], Frédéric Allegaert[1], Violeta Raverdy[2,3], Philippe Lefebvre[4], François Pattou[2,3], Bart Staels[4], Philippe Froguel[1,5], Amélie Bonnefond[1,5]

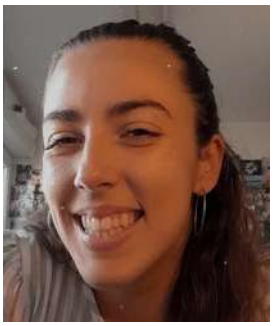
[1]Université de Lille, Inserm UMR1283, CNRS UMR8199, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, Lille University Hospital, Lille, France.
[2]Université de Lille, Inserm UMR1190, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, Lille University Hospital, Lille, France.
[3]Department of General and Endocrine Surgery, Lille University Hospital, Lille, France
[4]Université de Lille, Inserm UMR1011, Lille, France, European Genomic Institute for Diabetes (EGID), Institut Pasteur de Lille, Lille University Hospital, Lille, France.
[5]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom.

Somatic variants accumulate under chronic stress and may contribute to disease progression. Hyperglycemia is associated with increased somatic variant burden in blood. Here, we aimed to identify liver somatic coding variants in individuals with severe obesity and assess their association with key metabolic traits, particularly glycemic control.

We analyzed data from 306 individuals enrolled in the ABOS (Atlas Biologique de l'Obésité Sévère) study, all of whom had severe obesity and underwent liver biopsy during bariatric surgery. By combining whole-exome sequencing of blood-derived DNA with total RNA sequencing of liver tissue, we detected somatic coding variants in the liver. We assessed their burden across histological stages of liver disease and examined associations with metabolic traits, especially glycemic control. Mendelian randomization was used to test the causal relationship between metabolic traits and liver somatic variant burden.

The burden of liver somatic variants was significantly associated with higher glycemia, but only in individuals with metabolic dysfunction-associated steatohepatitis (MASH). We also found a causal role of hyperglycemia in promoting somatic variant accumulation in MASH. Notably, the most frequently mutated genes in hyperglycemic MASH (*i.e. HLA-G, AEBP1, HSPG2,PI4KA*) were involved in liver cancer.

These findings suggest a potential feed-forward loop linking metabolic stress, somatic mosaicism, and liver disease progression to MASH in individuals with severe obesity. They underscore the importance of glycemic control in MASH and support targeted treatment strategies in individuals with type 2 diabetes.



Salomé FARGE

The nuclear receptor Rev-erb-α controls atherosclerotic plaque neovascularization

Farge S[1], Bellengier C[1], Ferri L[1], Duhem C[1], Diedisheim M[2], Kara Ali G[1], Delhaye S[1], Sebti Y[1], Venteclef N[2], Staels B[1], Haas J[1], Tardivel M[3], Gauthier JF[2], Duez H[1] & Pourcet B[1]

[1]*Université de Lille, INSERM, IPL, EGID-U1011*
[2]*Université Paris Cité, INEM, INSERM-U1151*
[3]*Université de Lille, BiCeI-US41*

Plaque instability is the most deleterious atherogenic event, leading to plaque rupture and acute thrombosis. Among destabilizing processes, intraplaque neovascularization accelerates plaque progression, induces plaque rupture, and reduces statin benefits in humans. However, the underlying mechanisms remain understudied.

Using a multi-omics approach combined with laser microdissection on human endarterectomies from high- and low-cardiovascular-risk diabetic patients, we identified the nuclear receptor Rev-erb-α as an important regulator of plaque stabilization and intraplaque neovascularization. While Rev-erb-α has been studied in lipoprotein metabolism and inflammation, its role in intraplaque neovascularization has not been established yet. For that purpose, we developed a 3DISCO-based whole-organ imaging approach to analyze the intraplaque vessel content in brachiocephalic arteries from 18-months-old Rev-erbα$^{+/+}$ LDLr$^{-/-}$ and Rev-erbα$^{-/-}$ LDLr$^{-/-}$ mice fed a chow diet.

In this model, our transcriptomic analysis demonstrates that pro-angiogenic pathways are particularly upregulated in Rev-erbα deficient mice compared to control. Furthermore, we show in a scRNAseq experiment that dysfunctional activated luminal endothelial cells are particularly enriched in plaque from Rev-erbα$^{-/-}$ mice. Accordingly, Rev-erbα deficiency enhances the development of a more complex and immature intraplaque vascular network compared to control. Strikingly, intraplaque neovessels emerge from the lumen and from isolated and organized endothelial cells, suggesting an angiogenic and vasculogenic origin, usually induced by endothelial progenitor cells. *In vitro*, using genetic and pharmacological approaches, we identified Rev-erb-α as a key modulator of the pro-angiogenic program and the expression of genes involved in tip-stalk cell selection and EPC recruitment.

In conclusion, we identified the nuclear receptor Rev-erb-α as an inhibitor of intraplaque neovascularization, therefore Rev-erb-α represents a putative pharmacological target for stabilizing plaque in very high-cardiovascular-risk patients.

Tiffany GENCARELLI

Tools and Development of Cell Therapy for Parathyroid Auto-, Allo- and Xeno-Graft

Gencarelli T[1], Chetboun M[1,2], Thevenet J[1], Quenon A[1], Gibier JB[3], Gmyr V[1,4], Marciniak C[2], Baud G[2], Massaad L[2], Gobert M[2], Vantyghem MC[1,5], Hubert T[1], Caiazzo R[2], Kerr-Conte J[4], Hazzan M[6], Pattou F[1,2], Maanaoui M[1,6].

[1]Univ. Lille, Inserm, CHU Lille, Institut Pasteur Lille, U1190 - EGID, 59000, Lille, France
[2]CHU Lille, Department of General and Endocrine Surgery, F-59000, Lille, France
[3]CHU Lille, Department of Pathology, F-59000, Lille, France
[4]CHU Lille, Plateforme de Biothérapie, 59000, Lille, France.
[5]CHU Lille, Department of Endocrinology, Diabetology, and Metabolism, F-59000, Lille, France
[6]CHU Lille, Department of Nephrology, F-59000, Lille, France

Hypoparathyroidism is a rare yet debilitating endocrine disorder caused by insufficient parathyroid hormone (PTH) secretion, leading to chronic hypocalcemia and symptoms ranging from neuromuscular irritability to renal complications. When conventional therapies, calcium and vitamin D supplementation, recombinant PTH, or autotransplantation after accidental parathyroidectomy, fail or lose efficacy, innovative treatments are needed. Parathyroid allotransplantation emerges as a promising but still underdeveloped alternative.

My PhD project aims to develop and standardize protocols for parathyroid allotransplantation using either minced or enzymatically digested hyperplastic human parathyroid tissue from living donors. The digested tissue approach, inspired by pancreatic islet transplantation, offers key advantages such as injectability and graft standardization yet remains largely unexplored.

We compared minced versus digested tissues through in vitro and in vivo studies. In vitro, digested cells were cultured, phenotyped by flow cytometry, assessed for viability, apoptosis, and gene expression of CaSR, PTH, GCM2, and VDR. Functional perifusion assays confirmed calcium-dependent PTH secretion at day 5. Enzymatic digestion produced highly viable cells (≈96%) with minimal necrosis and preserved expression profiles, although a temporal downregulation was expected and observed.

In vivo, immunodeficient mice received renal subcapsular grafts of minced or digested tissue. Human PTH secretion was monitored over time, and histology at day 30 assessed endocrine volume, vascularization, fibrosis, and proliferation. Both graft types sustained PTH secretion and comparable integration, with less fibrosis observed in digested tissue. These findings confirm the feasibility and functionality of both strategies and highlight the potential of digested tissue for minimally invasive, injectable transplantation.

Future work focuses on intramuscular transplantation, with ongoing PET imaging to assess graft viability and preclinical studies in a minipig model to enable clinical translation. In 2024, France's first parathyroid retrieval from a deceased donor at Lille hospital, conducted as part of this project, marked a major milestone toward allogeneic parathyroid transplantation.

Margaux LEDUC

The Macrophage Clock Controls Skeletal Muscle Regeneration

M. Leduc[1]*, Q. Thorel[1]*, C. Duhem[1], S. Delhaye[1], B. Ram[1], C. Bellengier[1], A. Hebras[1], M. Bicharel[1], A. Mayeuf-Louchart[3], B. Pourcet[1], L. Ferri[1], F. Delahaye[2], A. Bonnefond[2], B. Staels[1], H. Duez[1] and Y. Sebti[1]

Univ. Lille, Inserm, CHU Lille, IPL, EGID, 59000 Lille, France, [1]U1011, [2]U1283/8199, [3]U1172

Scientific context: Skeletal muscle regeneration requires the well-orchestrated interaction between satellite cells (MuSC), fibro-adipogenic progenitors (FAPs) and immune cells, which provide the optimal microenvironment for the proliferation and differentiation of MuSC and FAPs. Among immune cells infiltrating the skeletal muscle, macrophages (Mϕ) are one of the most abundant and are crucial for this process after injury. The circadian clock controls various physiological processes, including immunity.

Objectives: The aim is to determine whether the clock controls skeletal muscle repair via circadian recruitment and/or Mϕ function, which are essential for orchestrating adequate tissue regeneration.

Materials and methods: C57/Bl/6J wild type mice were either injured during their resting phase (ZT6) or during their active phase (ZT18) and skeletal muscle regeneration was investigated through flow cytometry, histological, gene-expression analysis and single-nuclei experiments.

Results: We observed impaired muscle regeneration when mice are injured at ZT6 compared to ZT18, illustrated by smaller regenerated fibers and increased fibrosis. This result is associated with increased pro-inflammatory Mϕ recruitment compared to mice injured at ZT18. Interestingly, conditioned-media from Mϕ isolated from mice injured at ZT18 are more potent to induce myoblast differentiation than Mϕ isolated at ZT6. An unbiased single-nuclei RNA sequencing approach performed on mice injured at ZT6 and ZT18 have evidenced clock-regulated ligands secreted by Mϕ involved in the communication with FAPs and MuSC.

Conclusion and perspectives: Collectively, our results highlight the importance of the functional clock of the Mϕ in the control of skeletal muscle repair. In vivo experiments will help us to validate the implication of the different target in the circadian regulation of Mϕ and myoblast communication.

Gabriele MAGGIONI

Dynamic Prediction of 5-year weight Trajectories after Bariatric Surgery: an Adaptive Model for Postoperative Monitoring

Gabriele Maggioni[1], Violeta Raverdy[1], Philippe Preux[2], François Pattou[1]

[1]*Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1190- EGID, F-59000, Lille, France.*
[2]*Inria, Univ. Lille, CNRS, Centrale Lille, UMR 9198-CRIStAL, F-59000, Lille, France*

Background. Bariatric surgery is the most effective long-term intervention for sustained weight loss in severe obesity. Yet, postoperative weight trajectories are highly heterogeneous: while some patients achieve and maintain > 60% total weight loss (TWL), others experience early plateaus or substantial weight regain, undermining metabolic benefit. Early identification of patients at risk of poor outcomes is essential to personalize follow-up and optimize long-term success. Recent static machine learning models, such as SOPHIA, have enabled 5-year BMI prediction using easily accessible baseline variables (age, weight, diabetes, surgery type). Despite their utility, these models are inherently limited: their predictions are fixed preoperatively and cannot evolve with real postoperative data, failing to account for the patient's actual trajectory.

Methods. We developed a **dynamic, individualized, and probabilistic model** to predict 5-year weight trajectories, updating estimates as postoperative data accumulate. The model integrates the SOPHIA baseline structure with **sparse functional principal component analysis (PACE)** to capture latent TWL dynamics across the population. It supports irregularly spaced measurements, handles missing data, and can recalibrate predictions at any timepoint during the 5-year follow-up.

Results. Compared to static models, the dynamic framework improves prediction accuracy (smaller MAD up to 51% for 5 years prediction), narrows confidence intervals, and delivers real-time, patient-specific outputs. At any stage of follow-up and for each new point observed the model generates:
- **a predicted trajectory,**
- **uncertainty-aware confidence bands,**
- **individualized probability of surgical failure** (e.g. TWL <15%)

These features enable proactive adjustment of follow-up intensity and personalized intervention planning.

Conclusion. This is the **first dynamic model** designed to predict and continuously update 5-year weight loss trajectories after bariatric surgery. It marks a shift from static risk scoring toward **continuous, data-driven monitoring**, aligning with the principles of **precision medicine** and **digital twin systems**. The framework offers a scalable solution for clinicians to anticipate poor outcomes, engage patients in shared decision-making, and deliver tailored long-term care in bariatric surgery.

Amel MAKOUR

The Human Small Intestinal Microbiome is Linked with high-risk Diabetes and MASLD Subphenotypes

Amel Makour[*1,2,3], Benjamin Diel[*1,2,3], Violeta Raverdy[*6], Silvia Gschwendtner[4], Michael Schloter[4], Andreas L. Birkenfeld[1,2,5], François Pattou[+6], Reiner Jumpertz von Schwartzenberg[+1,2,3,5]

[1]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Germany
[2]German Center for Diabetes Research (DZD)
[3]M3 Research Center of the Medical Faculty of the University of Tübingen, Germany
[4]Research Unit for Comparative Microbiome Analysis, Helmholtz Center Munich, Germany
[5]Department of Internal Medicine IV, Division of Diabetology, Endocrinology and Nephrology, Eberhard-Karls University Tübingen, Germany
[6]Lille University – Lille University Hospital – Inserm U1190 – Institut Pasteur de Lille, France
**Contributed equally*
+Equaly contributing senior authors

Clinical sub-phenotypes of type 2 diabetes (T2D) and metabolic dysfunction associated liver disease (MASLD) have been identified and largely differ in the risk for complications. Yet, the underlying mechanism remains unclear. The human gut microbiota is one of the factors associated with obesity, insulin resistance and MASLD. Most studies investigate fecal samples from the large intestine, whereas the main site for nutrient absorption is the small intestine (duodenum, jejunum, and ileum) which is scarcely explored. This project shows the first comprehensive human jejunal microbiome data and its associations with host metabolic sub-phenotypes.

We collected jejunal content fluids from 627 individuals undergoing bariatric surgery with metabolic phenotyping. Clinical sub-phenotypes of patients were based on recently published algorithms. Microbial DNA was extracted using an optimized protocol for low-abundance biomasses to recover two dominant microbial kingdoms: bacteria and archaea. Quantification by standard qPCR is limited to a 3000 DNA copies detection limit, thus we rely on digital PCR that can detect up to 1 DNA Genome Copy (GC).

Absolute quantification of microbial DNA revealed an average of 31 x 10^3 bacterial GC/mL, with 42,78 % of samples yielding 10^2 to $<10^3$ copies, 41,31% yielding 10^3 to $<10^4$ copies, 9,6% from 10^4 to 10^5 copies and 6.2% from 10^5 to 1,3 x 10^6 bacterial genome copies. Archaea were also detected in small quantities with an average of 119 GC/mL, with 47.7 % of samples yielding values from 85 to <500 copies, 4.4 % from 500 to 1300 and 47.7% had no copies. In association with the clinical phenotypes we found that the high risk diabetes cluster (severe insulin resistant diabetes) had significantly higher GC for bacteria compared to the mild obesity-related cluster (median = 8039, IQR=60362 vs median= 1239, IQR= 4174, p= 0.025). Similarly, the cardiometabolic MASLD cluster had increased bacterial DNA abundance vs controls (median=1655, IQR=6078 in CM vs median=1141, IQR=2348 in controls, p=0.041), which was not observed for the liver-specific cluster. We did not observe associations of the clinical T2D or MASLD clusters with archaea abundance. These are the first in-depth human jejunal microbiome data, showing increased bacterial colonization of the small intestine in individuals with high-risk metabolic subphenotypes in T2D and MASLD.

Romina PACHECO-TAPIA

Biological Insights from a Validated data-driven Untargeted LC-HRMS Workflow: Application to Patient Samples in a Diabetes Study

Romina Pacheco-Tapia[1], Inés Castro-Dionicio[1], Coralie Berthier[2], Jean-Michel Lecerf[2], Amélie Bonnefond[1], Philippe Froguel[1,3], Francesc Puig-Castellví[1], Marc-Emmanuel Dumas[1,3,4]

[1]University of Lille, Lille University hospital, 59045, Lille, France ; INSERM U1283, CNRS UMR 8199, Institut Pasteur de Lille, 59045, Lille, France.
[2]Nutrition and Physical Activity Department, Institut Pasteur de Lille, Lille, France.
[3]Division of Systems Medicine, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, W12 0NN, United Kingdom.
[4]The Victor Phillip Dahdaleh Institute of Genomic Medicine, McGill University, Montréal, H3A 0G1, Canada

Untargeted metabolomics using LC-HRMS has become a powerful tool in clinical and translational research, yet standardized guidelines for method validation remain limited. Conventional validation relies on a small set of representative analytes, introducing bias when hundreds of metabolites are detectable. To address this, we propose a data-driven evaluation strategy that integrates metabolite coverage as an additional criterion.

Leveraging the GNPS public spectral library as an accessible alternative to chemical standards, we benchmarked 23 LC-HRMS methodologies from six metabolomic platforms on commercial human serum using a Vanquish Duo HPLC coupled to an Orbitrap Exploris™ 240. Iterative Data-Dependent Acquisition (DDA) was implemented alongside conventional DDA, increasing the number of unique annotated metabolites with high-quality fragmentation spectra by up to 50%. Overall, 1482 metabolites were annotated, with GNPS-based identifications validated against chemical standards, achieving >80% spectral similarity and 100% annotation confirmation rate when standards are available.

Building on this validated workflow, we analyzed serum from a clinical diabetes study, including both case–control and sex-stratified groups. Differential metabolite testing revealed 167 sex-associated significant metabolites and 14 significant metabolites in case–control comparisons (sex-adjusted). Notably, glucose and several microbial-derived metabolites were among the most significant, reflecting disease-specific and host–microbiome interactions.

This combined methodological and clinical framework highlights the utility of GNPS-based data-driven validation for untargeted LC-HRMS and demonstrates its capacity to uncover biologically and clinically relevant signatures in diabetes research.

Gianni PASQUETTI

NKX6.1: an Actionable Biomarker Directly Associated with Islet Function and Clinical Outcomes after Islet Transplantation

Pasquetti G[1], Thévenet J[1], Chetboun M[1], Amayene Amassogo C[1], Elias M[2], Rakotoarisoa L[3], Carlotti F[4], Vantyghem M.C[1], Pattou F[1] and Kerr-Conte J[1]

[1]*Université de Lille, France*
[2]*Hôpital Saint-Louis, Paris, France*
[3]*Hôpitaux Universitaires de Strasbourg, France*
[4]*LUMC, Leiden, The Netherlands*

Objectives. Islet transplantation is a validated therapy for type 1 diabetes but clinical outcomes remain heterogeneous. There is an unmet need for actionable biomarkers predicting islet graft potency before transplantation (tx). In this study, we leveraged a comprehensive set of clinical data and biological samples to explore the relation between human islet *NKX6.1* gene expression and islet tx outcomes.

Methods. The *NKX6.1* mRNA copy number was quantified by digital PCR in 114 clinical preparations to study its relationship with graft function in our nude mouse bioassay, primary graft function (PGF) in human recipients, and 10-year clinical outcomes. Transcriptomic profiles were compared between *NKX6.1*-high and *NKX6.1*-low islet preparations. Finally, to prove a direct causal link, glucose-stimulated insulin secretion (GSIS) and in vivo graft function in mice were assessed after *NKX6.1* knockdown by lentiviral shRNA, or after silymarin-induced *NKX6.1* overexpression, in islets prior to tx.

Results. The *NKX6.1* copy number in islets before tx was significantly correlated with graft function in mice, independently of islet volume, purity, and viability ($p<0.001$), and was higher in patients with good PGF ($p=0.007$). A correlation was observed in Lille Hospital ($p=0.020$) and validated in an external cohort ($p=0.028$). ROC curve analysis demonstrated the added predictive value of *NKX6.1* compared with islet volume alone for predicting PGF (DeLong test, $p < 0.001$). A multivariate Cox model showed that the *NKX6.1* copy number was correlated with graft success (adjusted HR [95% CI]: 0.63 [0.43–0.92], $p=0.017$) and insulin independence (adjusted HR [95% CI]: 0.70 [0.52–0.93], $p<0.01$) over 10 years. Compared to *NKX6.1*-low islets, *NKX6.1*-high islets showed significantly higher expression of β-cell–associated gene sets and significantly lower expression of gene sets detrimental to islet function. Targeted *NKX6.1* silencing in human islets prior to tx significantly impaired GSIS *in vitro* ($p=0.020$) and led to progressive graft failure in mice ($p=0.037$). Conversely, *NKX6.1* induction by silymarin significantly improved *in vivo* graft function ($p=0.028$).

Conclusion. Quantification of *NKX6.1* mRNA copy number in islets before tx could serve as a complementary release criterion to improve the functional quality of clinical islet preparations, particularly when islet mass is insufficient.

Francesc PUIG-CASTELLVÍ

Metabolome Richness and its Relevance to Obesity and Antibiotic Intake

Francesc Puig-Castellví[1,2], Man-yi Jia[2], Romina Pacheco-Tapia[1], Ema Mocsonokyova[2], Zhaojie Wang[1], Inés Castro-Dionicio[1], Mickaël Chevalier[1], Yuan Wang[2], METACARDIS Consortium, Philippe Froguel[1,3], Robert Glen[2], Sofia Kirke Forslund[4], Sara Vieira-Silva[5], Ulrike Loeber[4], Kanta Chechi[2], Petros Andrikopoulos[2], S.Dusko Ehrlich[6], Oluf Pedersen[7], Karine Clément[8], Marc-Emmanuel Dumas[1,2,9].

[1]INSERMU1283, CNRSUMR8199, Institut Pasteur de Lille, University of Lille, Lille University Hospital, Lille, France; [2]Section of Biomolecular Medicine, Division of Systems Medicine, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK; [3]Section of Genetics and Genomics, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK; [4]Experimental and Clinical Research Center, Charité Universitätsmedizin & Max-Delbrück Center, Germany; [5]Institute of Molecular Biology, Mainz, Germany; [6]Department of Clinical and Movement Neurosciences, University College London, UK; [7]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [8]Service de Nutrition, Hospital Pitie-Salpetriere, Sorbonne Université, Inserm, Institut National de la Santé et de la Recherche Médicale, INSERM, France; [9]McGill Genome Centre, McGill University, Montréal, Canada.

Obesity is largely influenced by lifestyle, dietary patterns, physical activity and gut microbiome alterations. In particular, the Bact2 enterotype, a distinct microbiome ecology that has been linked to obesity, is characterized by a proinflammatory functional profile and poor gene richness. Here, we introduce the concept of metabolome richness and show that the loss in microbiome richness in obese individuals mirrors a reduced number of detected metabolites in blood plasma in a METACARDIS study subset (N=859), which we replicated in FLORINASH (N=920). Food diversity, assessed using the Alternative Healthy Eating Index, was positively associated with metabolite richness. Correlation analyses revealed that metabolite richness is primarily driven by host-, diet-, and microbial-metabolites.

We then stratified metabolic richness by origin (i.e., diet, drug), and tested associations with lifestyle, clinical and metagenomic profiles, identifying significant contributions from pulse intake, kidney function and KEGG pathways. We further examined the structural similarity of the 1061 annotated metabolites using clustering derived from Tanimoto coefficients calculated from chemical fingerprints, and we observed that the metabolites disappearing in obesity shared structural similarities, as most of them were found in the same cluster. The cluster most strongly associated with metabolome richness was characterised by a large number of gut microbial and dietary compounds that contain a phenol group (i.e. polyphenols and phenylpropanoids). Individuals with higher diversity of these phenol-containing compounds reported fewer antibiotic courses over the previous five years and exhibited an anti-correlation with the presence of antibiotic resistance genes, suggesting that this group of metabolites may play a protective role against pathogenic bacteria.

Individuals with higher diversity of these phenol-containing compounds reported fewer antibiotic courses over the previous five years, suggesting a protective role of these metabolites against pathogenic bacteria.

Altogether, our results suggest that metabolome richness depicts the loss of a constellation of dietary and microbial protective metabolites in severe obesity, mirroring the collapse in microbiome gene richness, suggesting a gradual loss in bio- and chemodiversity in metabolic diseases.

Zeinab RAMMAL

Epigenetic Signatures of Aging and Insulin Sensitivity in Human Skeletal Muscle

Zeinab Rammal[1,2], Violeta Raverdy[2,3], Lucas Maurin[1,2], Bénédicte Toussaint[1,2], Souhila Amanzougarene[1,2], Mehdi Derhourhi[1,2], François Pattou[2,3], Amélie Bonnefond[1,2], Philippe Froguel[1,2,4], Amna Khamis[1,2].

[1]*Inserm UMR1283, CNRS UMR 8199, France.*
[2]*Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, EGID, F-59000 Lille, France.*
[3]*Inserm, Translational Research in Diabetes (U1190), Lille, France.*
[4]*Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom.*

Skeletal muscle is a central regulator of glucose metabolism and a major determinant of whole-body insulin sensitivity, yet the underlying epigenetic mechanisms remain poorly understood. Here, we investigated whether DNA methylation changes in skeletal muscle are associated with key metabolic traits and contribute to type 2 diabetes (T2D).

Method: Skeletal muscle biopsies were collected from 84 individuals (age range 27–45 years), and DNA was subject to DNA methylation using Illumina's MethylationEPIC arrays. Epigenome-wide association studies (EWAS) were performed to identify CpG sites associated with a range of phenotypic traits, including age, C-peptide (fasting, 30-min, 120-min), insulin (fasting , 30-min, 120-min), and glycemia (fasting, 30-min, and 120-min), HbA1C, C reactive protein and, HOMA2-IR. For each model, we adjusted for sex, BMI, HOMA2-IR, cell composition, and age (for all traits except age itself). Multiple testing correction was performed using the bacon method. To identify target genes associated with CpGs, we generated transcriptomic (RNA-seq) and genotyping (Illumina Omni 2.5M arrays) data from the same individuals.

Results: No significant associations were detected between skeletal muscle DNA methylation at individual CpG sites and insulin or other glycemic traits, indicating that peripheral insulin sensitivity may not be strongly reflected in the muscle methylome. However, we found that age was associated with the differential methylation of 119 CpGs including known age-related CpGs in *ELOVL2* and *FHL2*. Most age-associated CpGs were hypermethylated and enriched in 5' UTR, suggesting transcriptional regulation. Mapping these CpGs to nearby genes revealed 56 CpGs linked to approximately 98 nearby genes, with the majority targeting distal genes. These genes were enriched in pathways essential for muscle function, including: mitochondrial activity (*AURKAIP1*, *MRPL20*), calcineurin signaling (*FHL2*), muscle development and structural integrity (*XIRP1*, *FHOD1*), and glycolysis/metabolic regulation (*GAPDH*, *TBC1D1*) highlighting the potential impact of age-related methylation changes on metabolic capacity and, structural maintenance in skeletal muscle.

Conclusion: These findings demonstrate that skeletal muscle DNA methylation primarily reflects age-dependent molecular remodeling rather than interindividual differences in insulin sensitivity, providing insights into the molecular mechanisms linking aging to skeletal muscle decline.

Chaima TOUAIBI

Annotating the biotransformed metabolome based on studies of untargeted and semi-targeted metabolomics using UHPLC-HRMS

Chaima TOUAIBI[1], Romina PACHECO-TAPIA[1], Inés CASTRO[1], Francesc PUIG-CASTELLVI[1], Georgia Lorentzen[2], Zoe Hall[2], Philippe FROGUEL[1,2], Marc-Emmanuel DUMAS[1,2]

[1]EGID, UMR8199, Lille University
[2]Division of Systems Medicine, Department of Metabolism, Digestion and Reproduction, Imperial College London

The gut microbiota significantly influences human pathophysiology through metabolic interactions. Several metabolic diseases, including steatotic liver disease and diabetes, are associated with microbial metabolite biotransformations, such as sulfation, glucuronidation and various conjugation reactions. The systematic annotation of these modified metabolites remains a major challenge in metabolomics since they are not widely described in databases and reference standards are limited.

In this study, we developed an ultra-high-performance liquid chromatography and high-resolution mass spectrometry metabolomics strategy combining untargeted profiling and semi-targeted methods to identify specific neutral losses (NLs) of conjugated metabolites. Metabolomic profiling of the modified metabolome was performed on human serum samples using a Vanquish Duo Orbitrap Exploris™ 240, with different applied in-source fragmentation voltages (0V–50V) for the unmodified metabolites. The Orbitrap IQ-X Tribrid mass spectrometer was used to acquire (MS^n) data. Both systems were coupled with reverse-phase C18 chromatography and ran in positive and negative ESI mode. The processed feature list was analysed in R using a script to detect 34 types of modification. Manual curation was conducted to confirm the types of putative modifications.

Using the Orbitrap Exploris™ 240, we detected 11,928 features, including 462 unique annotated metabolites, after applying a reproducibility filter (CV% < 30). Of these, 165 are MSI level 1 and 297 are MSI level 2 metabolites. In positive mode, we detected 300 NLs signatures, 54 of which were identified. In negative mode, we detected 277 NLs signatures, of which 28 were annotated. Overall, we detected 26 and 27 types of modification in positive and negative modes, respectively. Focusing specifically on sulfated metabolites in negative mode, we proposed 20 new annotations of previously unknown metabolites, while 114 remain unidentified.

Our strategy improves the detection and identification of modified metabolites in human serum, increasing metabolic coverage and providing new insights into the dark metabolome. By applying this workflow to cohort samples, we aim to identify conjugated metabolites associated with cardiometabolic diseases and to gain a better understanding of microbial-host interactions.

Bénédicte TOUSSAINT

High-fat, high-sugar Diet Leads to Divergent effect on Transcriptome and Translatome across mice Metabolic Tissues

Bénédicte Toussaint[1], Frédérik Oger[1], Mehdi Derhourhi[1], Emmanuel Buse-Falay[1], Raphaël Boutry[1], Philippe Froguel[1,2] and Amélie Bonnefond[1,2]

[1]Univ. Lille, Inserm, CHU Lille, IPL, CNRS, U1283-UMR 8199 - EGID, F-59000 Lille;
[2]Dept. of Metab., Digestion and Reprod., Imperial College London; London

The effects of a high-fat, high-sugar (HFHS) diet on gene expression at the RNA level in metabolic tissues have been extensively characterized, particularly through transcriptomic approaches. However, the consequences of such dietary challenges on the translatome (i.e., the set of actively translated mRNAs) remain largely unexplored. Since changes in mRNA abundance do not always correlate with protein production, studying the translatome offers unique insights into the regulation of gene expression at the level of translation. Ribosome profiling (Ribo-seq) provides a powerful and innovative approach to capture this layer of regulation, overcoming many of the limitations inherent to mass spectrometry–based proteomics.

To explore this aspect, five mice were fed with an HFHS diet and five control mice were maintained on a standard chow diet (CD). After eight weeks, we collected liver, kidney, heart, and brown adipose tissue (BAT). We performed both Ribo-seq and RNA-seq and combining these approaches to investigate translational regulation in metabolic tissues. When we compared our results with published proteomic data, we found that although a majority of genes and proteins showed consistent regulation, a subset displayed transcriptomic profiles that did not follow the same trend. By examining generally overlooked genes (i.e., not differentially transcribed), we were able to detect not only expected and well-characterized genes (*Acadvl*, *Acat1*), but also known genes not previously investigated in these tissues (*Glyctk*), as well as unexpected candidates (*Nomo1*).

In this study, we demonstrate that translatome analysis reveals regulatory mechanisms that are not detectable at the transcriptome level and provides a more comprehensive understanding of the cellular response to metabolic disturbances induced by an HFHS diet.

Zhaojie WANG

Metabolome-Metagenome Network Analysis in the Context of Cardiometabolic Diseases

Zhaojie Wang[1], Francesc Puig-Castellví[1], Ema Mocsonokyova[2], Philippe Froguel[1,2], Robert Glen[2], Marc-Emmanuel Dumas[1,2]

[1]*European Genomics Institute for Diabetes, UMR 8199/1283, Lille, France*
[2]*Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK*

Cardiometabolic diseases, including type 2 diabetes and ischemic heart disease (IHD), are marked by low-grade inflammation, disrupted gut microbiome composition, and persistent shifts in circulating metabolites. Multi-omics approaches help unravel the complex interplay between microbial functions, host genes, and metabolites within a systems biology framework.

The gut microbiome plays a key role in human metabolism and disease, but experimentally testing host-microbiome interactions remains costly and complex. To address this, we developed a multi-organism, KEGG-based[1] metabolic network linking microbial species, functional genes (*e.g.*, enzymes), and metabolites into a topological framework for analyzing gene-metabolite connectivity.

We applied this workflow to data from a subset of the *MetaCardis* cohort (n = 1 241), including healthy individuals (n = 275) and patients with IHD (n = 372), profiled via metagenomics and metabolomics[2]. Using a multi-organism network incorporating 31 IHD-enriched microbial species and 224 IHD-associated serum metabolites, we performed topological and statistical analyses. Gene-metabolite pairs linked to IHD exhibited significantly shorter path distances than unrelated pairs (p = 0.004), suggesting that microbial enzymes from IHD-enriched taxa are functionally closer to the altered metabolites. Topological analysis identified high interconnectivity among indole-derived conjugates, branched-chain amino acids (*e.g.*, valine, leucine, isoleucine), and succinate. Enrichment analysis revealed enhanced D-amino acid turnover and secondary bile acid remodelling (p < 1e-5). These changes converge on key mechanisms, including reduced nitric oxide availability, oxidative stress, and epithelial barrier dysfunction, driving low-grade inflammation and insulin resistance, consistent with IHD pathophysiology.

These results suggest that IHD severity may be influenced by host–microbiome molecular interactions. Methodologically, this approach offers a novel framework to evaluate the likelihood of microbiome–host crosstalk in regulating human physiology.

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Elise WREVEN

Differential Roles of CB1R Signaling Pathways in the Regulation of Beta Cell Inflammation and Function during Insulitis

Elise Wreven[1], Jessica Ábalos Martínez[1], Valery Gmyr[1], Gianni Pasquetti[1], Nathalie Delalleau[1], Julien Thévenet[1], Anaïs Coddeville[1], François Pattou[1], Julie Kerr-Conte[1], Thomas Hubert[1], Isabel González Mariscal[1]

[1]*Inserm UMR1190 - Translational Research for Diabetes, Université de Lille, CHU Lille, Institut Pasteur de Lille, Inserm, European Genomic Institute for Diabetes, Lille, France.*

Insulitis, a hallmark pathological feature of autoimmune type 1 diabetes (T1D), characterized by the progressive infiltration of immune cells into the pancreatic islets, mainly lymphocytes such as T cells, B cells, and macrophages. This pro-inflammatory environment is associated with beta cell dysfunction before destruction. We recently described the cannabinoid receptor type 1 (CB1R), a Gαi protein–coupled receptor expressed in both beta cells and immune cells, as a key factor in the initiation of insulitis and, identified nitric oxide (NO) as a mediator of beta cell damage downstream of CB1R signaling. Recently a novel CB1R beta-arrestin biased antagonist, monlunabant, was evaluated in a phase 2a clinical trials for obesity with optimal resulst. Thus, we aim to dissect the downstream signaling pathways of CB1R —beta-arrestin versus Gαi—during the onset of insulitis for pharmacological application. Human islets were treated with increasing concentrations of either a dual CB1R/iNOS inhibitor (zevaquenabant or S-MRI-1867) or the beta-arrestin–biased antagonist monlunabant (also known as S-MRI-1891) in the presence of proinflammatory cytokines. Islet function and inflammation were assessed by glucose-stimulated insulin secretion (GSIS), Seahorse metabolic analysis, live-cell imaging, qPCR and ELISA. Both compounds reduced NO production. Monlunabant specifically decreased *IL1B* and *CXCL10* expression and secretion, whereas CCL2, was reduced uniquely by a nonbiased inverse agonist. Blocking iNOS alone did not affect cytokine or chemokine expression, suggesting that CB1R acts upstream of iNOS in this process. Both blockers preserved mitochondrial function, increasing maximal glucose-stimulated respiration and ATP production, and protected GSIS from cytokine-induced dysfunction. Distinctively, monlunabant did not enhance GSIS above control levels.
Together, these findings demonstrate that CB1R governs insulitis through distinct signaling mechanisms. Through, beta-arrestin–dependent signaling, CB1R regulates proinflammatory gene expression, and maintains metabolic and functional beta cell responses without overstimulation. Thus, monlunabant represents a promising therapeutic candidate to protect beta cells from inflammation-induced damage in T1D.

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