Tuesday September 26, 2023

Olympic Museum | Quai d'Ouchy 1, 1006 Lausanne

LIPIDS AS MEDIATORS OF CELLULAR AND ORGANISMAL FUNCTION

8h15-8h45 Welcome coffee and badge distribution

Opening

8h45 Francesca Amati

Session I - Cell biology

Chair: Ping-Chi Ho

9h00 Giovanni d'Angelo (Laboratory of Lipid Cell Biology, Swiss Federal Institute of Technology Lausanne EPFL, Lausanne, Switzerland)

The Lipotype hypothesis

9h35 Thomas Langer (Max-Planck-Institute for Biology of Ageing, Cologne, Germany)

Programming of Mitochondria by Proteolysis

10h10 Ammar Ebrahimi (The Aging and Muscle Metabolism lab, Department of Biomedical Sciences, University of Lausanne, Switzerland)

Mitobooster: A Novel Strategy for Inducing Mitophagy and Enhancing Cellular Homeostasis

10h25 Coffee Break

Session II - Clinical lipids research and adipocyte biology

Chair: Francesca Amati

11h00 Kirsty Spalding (Cell and Molecular Biology, Karolinska Institute, Stockholm, Sweden)

Adipocyte and lipid turnover in human adipose tissue

11h35 Matthijs K. C. Hesselink (Diabetes and Metabolism Research Group, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, The Netherlands)

Myocellular lipids and mitochondria in human insulin resistance; does it take two to tango?

12h10 Horia Hashimi (Laboratory of Systems Biology and Genetics, Ecole polytechnique Fédérale de Lausanne (EPFL) and Swiss Institute of Bioinformatics, Lausanne, Switzerland)

Mammalian adipogenesis regulators (Aregs) exhibit robust non- and anti-adipogenic properties that arise with age and involve retinoic acid signalling

12h25 Lunch & Poster session

Chair: Marlen Knobloch and Alexis Jourdain

Session III - New tools and new areas for lipids investigations

Chair: Carles Cantò

13h45 Laura Goracci (H-EcoTox Laboratory, Department of Chemistry, Biology and Biotechnology, University of Perugia, Italy)

Epilipidomics: current challenges and recent achievements

14h20 Marlen Knobloch (Department of Biomedical Sciences, University of Lausanne, Switzerland)

Lipid droplets in the brain: more important than previously thought?

14h55 Nicolas Goss (Metabolomics Platform, Faculty of Biology and Medicine, University of Lausanne, Quartier UNIL-CHUV, Lausanne, Switzerland)

Lipidome-wide association study across adipose tissue, liver and skeletal muscle: the effect of diet and bile acid metabolism

15h10 Coffee Break

Session IV – Membrane lipids and lipid droplets

Chair: Giovanni D'Angelo

15h45 Anne-Claude Gavin (Department of cell physiology and metabolism, University of Geneva, Switzerland)

Isoform- and cell-state-specific lipidation of ApoE

16h20 Alessia Perino (Laboratory of Metabolic Signaling, EPFL, Lausanne, Switzerland)

Hepatic lipid overload triggers biliary epithelial cell activation via E2Fs

16h35 Tobias Walther (Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York City, USA)

The Phase of Fat: Mechanisms and Physiology of Lipid Storage

17h10 Concluding remarks and award distribution

Chair: Francesca Amati

The meeting is kindly supported by:

FNSNF

Fondation de la Recherche en Biochimie

EMBO

VectorBuilder
Revolutionize Gene Delivery

STEMCELL™ TECHNOLOGIES

TALK ABSTRACTS

Session I - Cell biology

Giovanni d'Angelo
Laboratory of Lipid Cell Biology, Swiss Federal Institute of Technology Lausanne EPFL, Lausanne, Switzerland

The Lipotype hypothesis

Single-cell genomics techniques have allowed for the deep profiling of individual cells in multicellular contexts. These new technologies have enabled the building of cell atlases where hundreds of different cell types are 3ategorized according to their transcriptional and epigenetic states. These analyses have led to the depiction of detailed cell transcriptional landscapes that could be interpreted in terms of cell identity. Nonetheless, transcription represents only one regulatory axis in the establishment of cell phenotypes and functions and it is intuitively clear that post-transcriptional events crucially concur to cell identity in ways that cannot be simply derived from transcriptional profiles. Thus, the chemical composition of individual cells and the activity of metabolic pathways are likely as good descriptors of cell identity as transcriptional profiles are. Moreover, accumulating findings assign to metabolism an instructive role towards the establishment of cell identity, yet our understanding of the integration of transcriptional and metabolic programs in cell fate determination remains superficial. We have recently measured the lipidomes and transcriptomes of individual human dermal fibroblasts by coupling high-resolution mass-spectrometry-imaging to single-cell transcriptomics. We find that the cell-to-cell variation of specific lipid metabolic pathways contributes to the establishment of cell states involved in the organization of skin architecture. In fact, sphingolipid composition defines fibroblast subpopulations and sphingolipid metabolic rewiring drives cell state transitions. These data uncover a role for cell-to-cell lipid heterogeneity in the determination of cell states and reveal a new regulatory component to the self-organization of multicellular systems.

Thomas Langer
Max-Planck-Institute for Biology of Ageing, Cologne, Germany

Programming of Mitochondria by Proteolysis

Mitochondria are essential metabolic organelles and integral part of numerous cellular signaling pathways. Cellular signals determine the composition of the mitochondrial proteome and the metabolic output of mitochondria, which influence cell fate during development, cell differentiation, in ageing and disease. Mitochondrial proteases are emerging as central regulators of these adaptive responses. The i-AAA protease YME1L regulates in concert with the stress-activated peptidase OMA1 mitochondrial fusion via OPA1 and couples mitochondrial shape and metabolic function. mTORC1- and LIPIN1-dependent phospholipid signaling activates YME1L, which rewires the mitochondrial proteome to ensure the synthesis of pyrimidine nucleotides. YME1L mediated proteolysis

promotes growth of pancreatic ductal adenocarcinoma cells and preserves the self-renewal capacity of adult neural stem cells. The mitochondrial rhomboid protease PARL, an intramembrane cleaving serine peptidase, has been linked to the assembly of respiratory complex III, coenzyme Q synthesis, PINK1-Parkin dependent mitophagy and cellular resistance against apoptosis and ferroptosis. PARL-mediated processing promotes dual localization of the lipid transfer protein STARD7 to mitochondria and the cytosol, which ensures mitochondrial coenzyme Q synthesis and coenzyme Q transport to the plasma membrane to lipid peroxidation and ferroptosis.

Ammar Ebrahimi
The Aging and Muscle Metabolism lab, Department of Biomedical Sciences, University of Lausanne, Switzerland

Mitobooster: A Novel Strategy for Inducing Mitophagy and Enhancing Cellular Homeostasis

Mitophagy is a cellular process that involves the selective degradation and removal of damaged or dysfunctional mitochondria. It plays an important role in cellular homeostasis, maintaining energy balance and metabolism and preventing cellular stress. Impaired mitophagy has been implicated in the pathogenesis of several disorders, including neurodegenerative diseases and metabolic disorders. While there have been promising findings regarding the potential therapeutic applications of mitophagy modulation, the translation of these discoveries into clinical practice requires further research. This includes optimizing delivery methods, specifically targeting mitochondria, and assessing efficacy in proper models. The goal of this study was to design chimeric peptides (MitoBoosters) containing 3 different regions: 1. CPP for cell internalization, 2. MTS for Mitochondrial targeting, and 3. LC3 interacting region to recruit the autophagy machinery. Our results from electron microscopy, MitoKeima, Mito-GR and autophagosome reporter cell or zebrafish lines confirmed significantly increased mitophagy. We also confirmed biogenesis of mitochondria and higher mitochondrial respiration after the mitophagy stage in healthy and Parkinson disease patient-derived fibroblasts. Mitobooster treatment of cells resulted in lower mitochondrial and whole cell ROS levels even in combination with ferroptosis inducers compared to controls. We also investigated other potential applications for these peptides and our results show that these peptides can have cytoprotecting and exercise mimicking activity.

We believe that this novel strategy for peptide delivery and mitophagy induction, through the forced contact, i.e. the recruitment of autophagosome to mitochondria, can serve as a novel therapeutic strategy to tackle diseases with impaired mitochondria.

Session II – Clinical lipids research and adipocyte biology

Kristy Spalding
Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

Adipocyte and lipid turnover in human adipose tissue

Obesity, defined as an excessive accumulation of body fat, is considered one of the major health challenges facing the world today. Adipose tissue is not uniformly distributed throughout the body, with subcutaneous adipose tissue comprising approximately 80 percent of the total body fat. When subcutaneous adipose tissue storage capacity is exceeded, excess intra-abdominal (visceral) adipose tissue accumulates. Excessive lipid deposition into visceral and other ectopic tissues (e.g. liver, muscle and heart) leads to local inflammation and insulin resistance. Thus, body fat distribution, has an important impact on cardiometabolic disease. Multiple factors, including sex and age, impact on subcutaneous and visceral adipose tissue accumulation. We investigate how differences in adipose tissue turnover contribute to regional differences in the distribution of body fat by determining the age of fat cells and lipids in human subcutaneous abdominal and omental adipose tissue. Fat cell and lipid ages were measured by analysing the integration of 14C derived from nuclear bomb tests into genomic DNA and triglycerides, respectively. We identify fat cell and lipid removal rates as important factors contributing to regional, as well as sex, age and BMI differences in the fat mass. Such differences may be important determinants of obesity-associated metabolic complications.

Matthijs K. C. Hesselink
Diabetes and Metabolism Research Group, School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, the Netherlands

Myocellular lipids and mitochondria in human insulin resistance; does it take two to tango?

Compromised insulin sensitivity of skeletal is commonly being observed in obese sedentary individuals and is the hallmark in pathogenesis of type 2 diabetes. Intramyocellular lipids (IMCL), predominantly stored as lipid droplets (LDs) have long be accused to hamper proper insulin signaling and hence to contribute to insulin resistance. Although negative correlations between IMCL content and insulin sensitivity have been reported in obese individuals, data in trained athletes reveal that this correlation is unlikely to be causal. Rather, more detailed analysis of LDs in muscle revealed that size, number, and cellular (TI or TII muscle fibers) and subcellular (sarcolemmal vs intermyofibrillar) distribution of the LD's affect these associations. Also, the type of fatty acids stored in the LDs, the interaction of LDs with mitochondria and the coating of LDs with proteins involved in lipolysis and possibly mitochondrial tethering, seems to play a role in the association with insulin resistance. Over the years, the picture has emerged that a dynamic regulation of storage and release of fatty acids in and from LDs is a prerequisite for maintenance of insulin sensitivity. In this lecture,

the putative role of fatty acids originating from LD lipolysis in mitochondrial function and network maintenance and dynamics, will be discussed in the perspective of fat oxidative capacity, metabolic flexibility and insulin sensitivity.

Horia Hashimi
Laboratory of Systems Biology and Genetics, Institute of Bioengineering, School of Life Sciences, Ecole polytechnique Fédérale de Lausanne (EPFL) and Swiss Institute of Bioinformatics, Lausanne, Switzerland

Mammalian adipogenesis regulators (Aregs) exhibit robust non- and anti-adipogenic properties that arise with age and involve retinoic acid signalling

Adipose tissue (AT) expansion is a hallmark of obesity and critically influences the development of metabolic complications, calling for a better understanding of its regulation. We have identified a subpopulation of adipose stem and precursor cells (ASPCs) that deviate from the conventional ASPC definition. These cells, characterized by high CD142 expression, are termed adipogenesis regulators (Aregs) and exhibit anti-adipogenic properties through paracrine signalling. We demonstrated the robust anti-adipogenic capacity of Aregs in various culture conditions and mouse strains ex vivo as well as in vivo using implantation models. Notably, Aregs hindered human ASPC differentiation, indicating a conserved mechanism across species. Transcriptomic and proteomic analyses followed by experimental validation ex vivo revealed that CD142 itself and MGP in cooperation with the retinoic acid pathway are responsible for Aregs' anti-adipogenic signalling. Moreover, ASPCs exposed to Aregs displayed an "Areg-like" transcriptomic signature suggesting that Aregs' activation can amplify their action by transforming neighbouring ASPCs into negative adipogenic regulators. We further identified that in mouse subcutaneous AT Aregs' phenotype acquisition is largely controlled by weaning: Aregs are highly adipogenic before weaning and non adipogenic after. However, early weaned mice display and "adult-like" phenotype thus underlining the role of nutrient and hormonal cues in Areg function.
In summary, this research characterized the molecular signals by which Aregs repress adipogenesis. Our research also opens new avenues regarding the regulatory mechanisms governing the acquisition of Aregs functional characteristics in ASPCs, and consequently define the way in which AT will grow in response to nutrient intake.

Session III – New tools and new areas for lipids investigations

Laura Goracci
H-EcoTox Laboratory, Department of Chemistry, Biology and Biotechnology, University of Perugia, Perugia, Italy

Epilipidomics: current challenges and recent achievements

Recent progress on analytical platforms for lipidomics has facilitated untargeted approaches and the investigation of low abundant lipid species. Consequently, epilipidomics, that is the study of modified lipids, is now a rapidly growing research field. Epilipids are formed by a range of enzymatic and non-enzymatic reactions that introduce structural modifications and/or new functional groups in the native molecule. Concerning their biological function, they are known to play crucial roles in physiological and pathological condition. Although a number of epilipid species have been extensively studied over the past decades (e.g., eicosanoids), our current knowledge about the entire epilipidome and its biochemistry is still very limited due to experimental and computational obstacles. Here, current challenges in epilipidomics will be discussed together with potential solutions. In addition, recent achievements on the biological roles of epilipids will be described.

Marlen Knobloch
Department of Biomedical Sciences, University of Lausanne, Lausanne, Switzerland

Lipid droplets in the brain: more important than previously thought?

Lipid droplets (LDs) are at the center stage of lipid metabolism and critical players in health and disease. Emerging evidence suggests that LDs also play a role in various brain cells and might even be linked to neurodegenerative diseases. However, studying LDs in the brain is challenging: Most LD-studies *in vivo* rely on staining methods, working poorly and providing only a static picture. I will talk about how LD-availability affects neural stem cells, and present our newly developed endogenous LD-reporter mouse (tdTom-Plin2), which enables staining-free fluorescent LD-visualisation in living and fixed tissues and cells. Using this tdTom-Plin2 mouse, we could show that LDs are present to a much larger extent than previously thought in various cells in the healthy brain. I will illustrate the power of this novel model using fluorescent-activated cell sorting (FACS) of cells which accumulated LDs, by live-imaging of LDs in embryonic brain sections and show how tdTom-Plin2 LDs change with high fat diet. As Plin2 is ubiquitously expressed and specifically localized to LDs, our tdTom-Plin2 mouse serves as a novel tool to study LDs and their dynamics in all tissues expressing Plin2 and provides a unique possibility to further study the role of LDs in the brain.

Nicolas Goss
Metabolomics Platform, Faculty of Biology and Medicine, University of Lausanne, Quartier UNIL-CHUV, Lausanne, Switzerland

Lipidome-wide association study across adipose tissue, liver and skeletal muscle: the effect of diet and bile acid metabolism

The organismal lipidome is remarkably diverse and its composition and abundance are determined by tissue-specific de novo synthesis and metabolization of external lipid sources, mainly from food intake. Lipid profiles were shown to be organ-specific, however the relative abundance and diversity of lipid species were not comprehensively investigated regarding the tissue function, effect of diet and bile acid levels. Bile acids have been recognized as enterohepatic-derived hormones which control lipid metabolism and global metabolic health. In the present study we first evaluated the relative distribution and diversity of lipid species across four organs playing a central role in the lipid energy metabolism (including lipid synthesis, utilisation, and storage): subcutaneous white adipose tissue (scWAT), brown adipose tissue (BAT), skeletal muscle (i.e., quadriceps) and liver. Furthermore, we aimed to determine the effect of diet on lipid composition of specified organs obtained from C57BL/6J mice fed with chow diet (CD) and high-fat diet (HFD). The mice (all males) were sacrificed at 29 weeks of age, following a period of 21 weeks on CD or HFD. The sacrifice was performed in the postprandial state (4h after physiological refeeding). Tissue lipidome was characterized using a high-coverage, highly sensitive and specific targeted SRM-based methodology coupled to HILIC separation mode. The sample preparation workflow consisted of tissue lysis and single-step extraction with isopropanol. More than 2400 lipid species were screened in the initial qualitative analysis (in multiple runs) followed by quantification of robustly detected species. Lipid quantification was achieved by a single point calibration with 75 isotopically labelled standards representative of different lipid classes, covering lipid species with diverse alkyl chain lengths and unsaturation degrees. Correction of isotopic overlap was performed using LICAR (https://slinghub.shinyapps.io/LICAR/). As a result, a wide panel of 24 lipid classes comprising 533 to 838 lipid species were quantified (CV<20%) depending on tissue type. Additionally, bile acids (15 species) were quantified in mice liver and plasma using stable isotope dilution approach.

Highest diversity of lipids was detected in quadriceps (n=838 species) while white adipose tissue contained the lowest (n=533 species) number of species. Main differences were found for triacylglycerols (TG) and glycerophospholipids such as glycerophosphocholines (PC) and glycerophosphoethanolamines (PE). In mice fed with HFD, we observed the accumulation of TG as a general trend for all tissues. Besides, a decreasing trend of some hexosylceramides (HexCer), and sphingomyelins (SM) was reported in a tissue-specific manner. The dataset is currently under investigation to identify the lipid signatures associated with measured physiological parameters including body and organ weight, blood glucose and bile acid levels.

Session IV – Membrane lipids and lipid droplets

Anne-Claude Gavin
Department of cell physiology and metabolism, Centre Medical Universitaire, University of Geneva, Geneva, Switzerland

Isoform- and cell-state-specific lipidation of ApoE
Lipids have long been the focus of scientific attention. They provide essential functions and contribute to the organization of eukaryotic cells. I will explain how we combine biochemistry, mass spectrometry and bioinformatics tools to map protein-lipid interactions and thus better understand how lipid transport between cell membranes ensures their proper communication. APOE lipoprotein is the main lipid transporter in the brain and an important player in neuron-astrocyte metabolic coupling. We will see how APOE polymorphism and metabolic stress factors affect APOE lipidation in astrocytes, and how these mechanisms lead to loading APOE with an inappropriate (in the context of the brain) lipid, triacylglycerol.

Alessia Perino
Laboratory of Metabolic Signaling, EPFL, Lausanne, Switzerland

Hepatic lipid overload triggers biliary epithelial cell activation via E2Fs
During severe or chronic hepatic injury, biliary epithelial cells (BECs) undergo rapid activation into proliferating progenitors, a crucial step required to establish a regenerative process known as ductular reaction (DR). While DR is a hallmark of chronic liver diseases, including advanced stages of non-alcoholic fatty liver disease (NAFLD), the early events underlying BEC activation are largely unknown. Here, we demonstrate that BECs readily accumulate lipids during high-fat diet feeding in mice and upon fatty acid treatment in BEC-derived organoids. Lipid overload induces metabolic rewiring to support the conversion of adult cholangiocytes into reactive BECs. Mechanistically, we found that lipid overload activates the E2F transcription factors in BECs, which drives cell cycle progression while promoting glycolytic metabolism. These findings demonstrate that fat overload is sufficient to reprogram BECs into progenitor cells in the early stages of NAFLD and provide new insights into the mechanistic basis of this process, revealing unexpected connections between lipid metabolism, stemness, and regeneration.

Tobias C. Walther & Robert V. Farese, Jr.
Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York City, United States

The Phase of Fat: Mechanisms and Physiology of Lipid Storage
All organisms face fluctuations in the availability and need for metabolic energy. To buffer these fluctuations, cells use neutral lipids, such as triglycerides, as energy stores. We will present our current work on the molecular processes that govern the synthesis of energy storage lipids as well as their storage in and mobilization from lipid droplets.