LIPIDS AS MEDIATORS OF CELLULAR AND ORGANISMAL FUNCTION

8h30-8h45 Welcome 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 Short talk

10h25 Coffee Break

Session II - Clinical lipids research and adipocyte biology

Chair: Francesca Amati

11h00 Kristy 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 Short talk

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 Short talk

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 Short talk

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 awards distribution

Chair: Francesca Amati

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.

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.

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.

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.

Tobias C. Walther and 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.