Recruiting Mini-symposium on Metabolism
room AI 1 153, EPFL, Lausanne, Switzerland, December 14, 2017

Speaker: Dr. J. Andrew Pospisilik, Max-Planck Institute of Immunobiology and Epigenetics, Freiburg (D)

Title: Stochastic, Bi-Stable and Intergenerational Epigenetics in Metabolism and Disease

Abstract:
Metabolic disease currently impacts beyond 1 billion people. Rates are rising with childhood obesity having more than doubled in the last decade. This rapid rise in early life disease carries long-term health burden including heart disease, diabetes and stroke, making the issue one of the world’s chief economic and health care challenges of the day. While numerous studies have established a genetic framework for understanding metabolic disease, the contribution of critical regulatory layers, in particular epigenetic regulation, remain poorly understood. Our focus couples epigenomic analysis with functional genetics in mice to understand chromatin-coupled disease events and their direct implications for disease etiology. Recently, these efforts have uncovered novel roles for Polycomb silencing in buffering beta-cell dedifferentiation, as well as signalling modules that drive and potentiate beiging and browning of adipose tissues. They have also revealed mechanistic underpinnings for intergenerational control of non-genetic variation and what we believe to be the first stochastic disease ‘switch’ yielding distinct phenotypic ‘on’ and ‘off’ states in mouse and man. The data suggest the existence of polyphenism in mammals and have a profound influence on how we understand evolution and the genetic basis of phenotypic variation and disease.
Speaker: Prof. Olaia M. Naveiras, EPFL & Lausanne University Hospital (CHUV), Lausanne (CH)

Title: Metabolic Regulation of Hematopoietic Stem Cells and their Niche

Abstract:

Hematopoietic Stem Cells (HSCs) reside within the bone marrow (BM) where they are responsible for producing almost $10^{12}$ blood cells per day. In order to appropriately maintain their stemness while continuously producing astonishing numbers of mature cells, HSCs and their progeny establish an intricate crosstalk with the BM stroma that constitutes the HSC microenvironment or “niche”.

Although often ignored, adipocytes constitute the most abundant cell type within the human BM stroma, but little is known about their biological function or how they relate to other adipose depots in the body. BM adipocytes are most abundant in the long bones of the skeleton, and they increase dramatically in all locations with age, after chemo- or radiotherapy, or in obese individuals. Indeed, we were first to demonstrate that adipocytes are not passive space fillers of the marrow space, but that they actively inhibit the proliferation of blood progenitors. Given that NAD+ boosting strategies can revert the metabolic effects of high-fat induced obesity, we tested whether NAD+ boosters could increase blood progenitors in the BM, and found that Nicotinamide Riboside efficiently accelerates hematopoietic recovery through increased mitochondrial recycling.

Current work in the laboratory focuses on understanding how specific populations of BM adipocytes induce HSC quiescence. Given the fragility of mature adipocytes and the added challenge of isolating them from within the bone compartment, the laboratory has also focused on quantitative tool development for the study and isolation of BM adipocytes. Overall, our work has the potential to generate new niche-directed strategies to decrease the high mortality associated to the slow blood recovery after HSC transplantation for leukemia, and to unravel more general mechanisms of organ plasticity via reversible adipocyte infiltration.
Speaker: Dr. J. Gray Camp, Max-Planck Institute for Evolutionary Anthropology, Leipzig (D)

Title: Multilineage Organoids to Reconstruct Uniquely Human Development

Abstract:
Human pluripotent stem cells (PSCs) can self-organize into complex, three-dimensional (3D) tissues that recapitulate morphological, functional, and genetic aspects of human organ development. I will tell you about two areas where we are using organoids to understand human development, disease, and evolution.

First, we use single-cell transcriptomics to dissect 3D multilineage liver organoids generated by reconstituting hepatic, mesenchymal, and endothelial cell interactions occurring during liver bud (LB) development. We compare hepatocyte-like lineage progression from pluripotency in 2D culture and 3D LB organoids and find that organoid hepatoblasts diverge from the 2D lineage and mature into hepatocytes with a striking correspondence to fetal liver hepatocytes. We use a receptor-ligand pairing analysis and high-throughput chemical perturbation experiment to investigate how inter-lineage communication can impact hepatic maturation in the 3D microenvironment. I will also present preliminary efforts using multilineage organoids to understand dysregulated gene networks in cholesteatosis and pancreatic cancer.

Second, we use great ape organoids to reconstruct uniquely human development. Humans diverged from our closest living relatives, chimpanzees and other great apes, 6-10 million years ago. Since this divergence, our ancestors acquired genetic changes that enhanced cognition, altered metabolism, and endowed our species with an adaptive capacity to colonize the entire planet and reshape the biosphere. We have generated human, chimpanzee, orangutan, and macaque cerebral organoids and have identified cis-regulatory, gene expression, and cell biological features specific to humans. I will tell you about our plans to study the function of these human-specific genetic changes that set modern humans apart from our closest evolutionary relatives as well as all other organisms on the planet.
Speaker: Dr. Nora Vögtle, University of Freiburg (D)

Title: Integrative Approaches to Decipher Novel Roles of the Mitochondrial Presequence Processing Machinery in Health and Disease

Abstract:
The mitochondrial presequence processing machinery plays an essential role in mitochondrial protein biogenesis and proteostasis: its proteolytic components cleave N-terminal targeting peptides for protein maturation, remove destabilizing residues to increase the protein’s half-life and degrade toxic cleaved presequences. As 70% of all mitochondrial proteins are clients of this machinery dysfunctions result in an imbalanced mitochondrial proteome and mutations have been linked to neurodegeneration and cardiomyopathy. We have identified novel components and functions of the presequence processing machinery and pathophysiological mechanisms that link it to Alzheimer’s disease. For our studies we are using yeast as a model for detailed mechanistic analysis of these highly conserved processes as well as tissue culture and patient samples to investigate the impact of disease-related mutations on mitochondrial function and metabolism in human cells.
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Speaker: Dr. Giovanni D'Angelo, Institute of Protein Biochemistry, Naples (I)

Title: Glycosphingolipid Metabolic Reprogramming Drives Neural Differentiation

Abstract:
Neural development is accomplished by differentiation events leading to metabolic reprogramming. Glycosphingolipid metabolism is reprogrammed during neural development with a switch from globo to ganglio-series glycosphingolipids production. Failure to execute the glycosphingolipid switch leads to neurodevelopmental disorders in humans, indicating that glycosphingolipids are key players in this process. Nevertheless, both the molecular mechanisms that control the glycosphingolipid switch and its function in neurodevelopment are poorly understood. Here, we describe a self-contained circuit that controls glycosphingolipid reprogramming and neural differentiation. We find that globo-series glycosphingolipids repress the epigenetic regulator of neuronal genes expression AUTS2. AUTS2 in turn, binds and activates the promoter of the first and rate limiting ganglioside producing enzyme GM3 synthase, thus fostering the synthesis of gangliosides. By this mechanism the globo-AUTS2 axis controls glycosphingolipid reprogramming and neural genes expression during neural differentiation, which involves this circuit in neurodevelopment and its defects in neuropathology.