EPFL BioE Talks
minisymposium on metabolism

Monday October 2 2023

13h00 - 17h30
EPFL SV1717

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The Salk Institute for Biological Studies
San Diego CA (USA)

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Kristina Schoonjans
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Lausanne (CH)

Armand Kurum
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Johan Auwerx
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Institute of Bioengineering (IBI)
https://bioengineering.epfl.ch
EPFL BioE Talks Series
zoom link go.epfl.ch/EPFLBioETalks

Program

13:00-13:05	Introduction (Johan Auwerx)
13:05-13:45	**Kristina Schoonjans** (EPFL; Switzerland) *A systems genetics approach to identify novel determinants of bile acid homeostasis*
13:45-14:25	**Ronald M. Evans** (*Salk Institute; USA)* *Colon Cancer Checks in When Bile Acids Check Out*
14:25-15:05	**Christian Metallo** (*Salk Institute; USA)* *Dysregulation of amino acid and sphingolipid metabolism in co-morbidities of diabetes*
15:05-15-30	Coffee Break
15:30-16:10	**Johan Auwerx** (EPFL; Switzerland) *Ceramide de novo synthesis links muscle disorders with mitochondrial and protein Homeostasis*
16:10-16:50	**Giovanni D'Angelo** (EPFL; Switzerland) *The Lipotype Hypothesis*
16:50-17:30	**Armand Kurum (**EPFL; Switzerland) *Cancer-cell stiffening via cholesterol depletion enhances immunotherapy*

A systems genetics approach to identify novel determinants of bile acid homeostasis

Kristina Schoonjans

Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Abstract

Bile acids (BAs) are complex enterohepatic hormones that control whole-body metabolism. To unravel novel regulators of BA homeostasis, we used an integrated system genetics approach on the BXD genetic reference population. We quantified postprandial BAs in liver, feces, and plasma of 360 mice fed chow or high-fat diet and determined that both genetics and diet strongly influence BA pool size, composition, and correlation with metabolic traits. We also mapped hundreds of quantitative trait loci that modulate BAs and identified *Ces1c* as a genetic determinant of plasma tauro-ursodeoxycholic acid (TUDCA), a BA with established disease-preventive actions. The association between *Ces1c* and TUDCA was validated using data from independent mouse cohorts and a *Ces1c* knock-out mouse model. Collectively, our data are a unique resource for dissecting the physiological importance of BAs as determinants of metabolic traits, as underscored by the identification of CES1c as a master regulator of plasma TUDCA levels.

Colon Cancer Checks in When Bile Acids Check Out

Ronald M. Evans

Professor at the Salk Institute for Biological Studies,
March of Dimes Chair in Developmental and Molecular Biology

Abstract
The discovery of the bile acid receptor FXR launched a new branch of physiology which demonstrated bile acids are not simply digestive surfactants but also act as potent hormones by controlling metabolic gene networks. Indeed, high levels of FXR expression in gut, liver, kidney, adrenal, gall bladder, stomach and adipose makes it a potent regulator of body-wide metabolism. Unexpectedly, we found that selective activation of intestinal FXR both protects mice against diet-induced weight gain and lowers colorectal cancer progression. This impact on cancer led us to next explore FXR's potential to manage the increasing prevalence of Inflammatory Bowel Disease(IBD) which includes Ulcerative Colitis and Crohn's Disease. Finally, I'll also show how FXR signaling modulates the microbiome and the role of the microbiome and reciprocally the role of the microbiome in modulating bile acid signaling.

Dysregulation of amino acid and sphingolipid metabolism in co-morbidities of diabetes

Christian Metallo

Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies

Abstract

Metabolism is central to virtually all cellular functions and contributes to a range of diseases. A quantitative understanding of how biochemical pathways are dysregulated in the context of diseases such as cancer, metabolic syndrome, and neuropathy is necessary to identify new therapeutic targets. To this end we apply stable isotope tracers, mass spectrometry, and metabolic flux analysis (MFA) to explore metabolism in cells, animal models, and human patients. We are particularly interested in understanding how amino acid and sphingolipid metabolism are coordinated in the context of cancer and diabetes. Serine, glycine and one carbon metabolism is critically important for cell function and health, but the amino acids associated with this pathway are commonly reduced in patients with metabolic syndrome. Here I will detail how we apply MFA and related methods to decipher why serine and glycine are reduced in mouse models of diabetes. Similarly, restricting dietary serine and glycine in a high-fat diet promotes sensory neuropathy in C57BL/6 mice. In turn, supplementation of serine improves sensory function in diabetic animals, suggesting potential therapeutic strategies for treating patients with serine-associated neuropathy. These symptoms are similar to that experienced by patients with hereditary neuropathy caused by non-canonical sphingolipid accumulation, highlighting a mechanistic role for sphingolipid metabolism in peripheral neuropathy. These data provide insights into potential drivers of diabetes co-morbidities and the role of amino acids and sphingolipids in neuropathy.

Ceramide de novo synthesis links muscle disorders with mitochondrial and protein Homeostasis

Johan Auwerx

Laboratory of Integrative Systems Physiology, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

Abstract

Aging and muscular dystrophies share common pathological features typified by impaired mitochondrial bioenergetics and protein homeostasis. However, underlying factors governing these failures are poorly understood. We identify here elevated ceramide biosynthesis as a unifying characteristic in aged and dystrophic skeletal muscle. Analysis of a large-scale skeletal muscle gene expression compendia and human genetic data identifies Sptlc1, the rate limiting enzyme of the ceramide de novo synthesis pathway, as the main contributing factor. Pharmacological or genetic inhibition of Sptlc1 reverses key morphological and functional hallmarks of skeletal muscle aging and dystrophy. These improvements are paralleled by restoration of mitochondrial function and proteostasis across worm, mouse and human skeletal muscle aging, suggesting a reciprocal link between ceramides, mitochondrial function and protein aggregation. Collectively, our data show that suppressing ceramide biosynthesis may be a potential therapeutic approach to combat muscle diseases and aging via mitochondrial and proteostasis remodeling.

The Lipotype Hypothesis

Giovanni D'Angelo

Laboratory of Lipid Cell Biology, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

Abstract

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 categorised 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 axis in the establishment of cell phenotypes and functions and 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 lipid metabolism an instructive role towards the establishment of cell identity, yet our understanding of the integration of transcriptional and lipid metabolic programs in cell fate determination remains superficial. Here I will report on our attempts to investigate lipidomes at single cell levels and at high spatial resolution by MALDI imaging mass spectrometry.

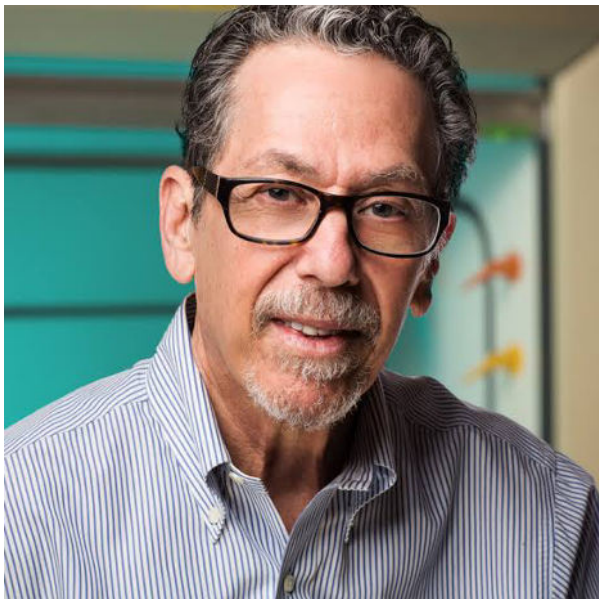
Cancer-cell stiffening via cholesterol depletion enhances immunotherapy

Armand Kurum

Laboratory of Biomaterials for Immunoengineering, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland

Abstract

Malignant transformation is associated with biochemical changes, such as downregulation of antigen presentation and upregulation of immune inhibitory receptors, and biomechanical changes, such as cancer-cell softening. While altered signaling on the cancer-cell surface has been intensively studied in the past decades, little is known about the influence of cancer-cell biomechanics on the immune response. Here, we show that soft cancer cells have enhanced accumulation of cholesterol in the plasma membrane (PM). PM cholesterol depletion led to a reorganization of the actin cytoskeleton at the cortex and stiffened cancer cells. The stiffening intervention potentiated the immune responses of T-cells and Natural Killer (NK) cells in vitro and in vivo.



Ronald M. Evans, Ph.D. is a Professor at the Salk Institute for Biological Studies, where he holds the March of Dimes Chair in Developmental and Molecular Biology. He is known for pioneering studies on hormones' normal activities and their roles in disease. A major discovery was nuclear hormone receptors, which respond to steroid hormones, vitamin A, vitamin D, thyroid hormones and bile acids. By targeting genes these receptors help control sugar, salt, calcium, cholesterol and fat metabolism. They are primary targets in breast, prostate and pancreatic cancers and leukemia treatment, and have therapeutic roles in chronic inflammation, osteoporosis and Type 2 diabetes and asthma. His muscle metabolism studies led to the discovery of exercise mimetics, which promote the benefits of fitness without training. Exercise mimetics will help battle the obesity epidemic, diabetes, heart disease and frailty. Evans co-led 4 Stand Up to Cancer Dream Teams and was a Lustgarten Distinguished Scholar (2014-2019). He was awarded the Albert Lasker Basic Medical Research Award in 2004 and the Wolf Prize in Medicine in 2012. He is a member of the NAS, NAM and NAI.

Christian Metallo is a professor at the Salk Institute and holds the Daniel and Martina Lewis Chair. He is an adjunct professor of Bioengineering at UC San Diego. His laboratory integrates engineering approaches, stable isotope tracing, mass spectrometry, and molecular biology tools to dissect how metabolic dysregulation contributes to human disease. Key focus areas include cancer, macular disease, neurodegeneration, and diabetes. Christian received his Ph.D. in Chemical Engineering from the University of Wisconsin-Madison and was an American Cancer Society Postdoctoral Fellow at the Massachusetts Institute of Technology before starting his lab at UC San Diego in 2011.