Thursday June 1, 2017
SwissTech Convention Center
EPFL, Lausanne

……

LIMNA Symposium: Metabolism Research in Switzerland

……

Organizing Committee: Prof. J. Auwerx, Prof. B. Desvergne, Prof. L. Fajas, Prof. F. Pralong, Prof. B. Thorens, Prof. K. Sakamoto and Dr. L. Descamps.

Sponsored by

Invited Speakers

- **Dr. Carles Cantó,** Nestlé Institute of Health Sciences, Switzerland.
- **Prof. Roberto Coppari,** Department of Cell Physiology and Metabolism, University of Geneva, Switzerland.
- **Prof. Lluis Fajas,** Center for Integrative Genomics, University of Lausanne, Switzerland.
- **Prof. Michael N. Hall**, Biozentrum, University of Basel, Switzerland.
- **Prof. Wilhelm Krek,** Institute for Molecular Health Sciences, ETH Zürich, Switzerland.
- **Prof. Jean-Claude Martinou**, Department of Cell Biology, Faculty of Sciences, University of Geneva, Switzerland**.**
- **Prof. Umberto Simeoni**, University Hospital of Lausanne (CHUV), Switzerland.
- **Prof. Markus Stoffel,** Institute for Molecular Health Sciences, ETH Zürich, Switzerland.
- **Prof. Christian Wolfrum,** Department of Health Sciences and Technology, ETH Zürich, Switzerland.

Agenda

8h30-9h00 Welcome and distribution of badges

Opening

9h00 *Welcome*

Morning session

Chairman:

9h10 **Markus Stoffel**
"Posttranscriptional regulation of metabolism"

9h45 Roberto Coppari
"Life Without Insulin: Is this possible?"

10h15 Coffee Break

Chairman:

10h35 Michael N. Hall
" mTOR signaling in growth and metabolism"

11h10 **LLuis Fajas**
"cdk4 signaling in growth and metabolism"

11h40 **Wilhelm Krek**
"HIF signaling, alternative splicing and fructose metabolism in cancer "

12h10 Lunch

Afternoon session

Chairman:

13h10 Poster session

14h10 Christian Wolfrum
"Brown and brite fat - how do they contribute to metabolic control"

14h40 Carles Cantó
"Mitochondrial dynamics in the control of brown adipose tissue thermogenic function"

15h10 **selected talk**
15h25 **selected talk**
15h40 **selected talk**

15h55 Coffee Break

Chairman:

16h15 Jean-Claude Martinou
"The mitochondrial pyruvate carrier in neurons and cancer cells: to carry or not to carry"

16h45 Umberto Simeoni
"Developmental origins of metabolic diseases: between genome and early environment"

17h15 Concluding remarks and poster prize distribution

INVITED SPEAKERS ABSTRACTS

Roberto Coparri
Department of Cell Physiology and Metabolism, University of Geneva, Switzerland.

Life Without Insulin: Is this possible ?

The notion that life without insulin is not possible has recently been challenged. In fact, results from different laboratories convincingly indicated that life without insulin is possible in rodent models of insulin deficiency provided that these are treated with leptin monotherapy. We have identified specific hypothalamic leptin-responsive neurons that have the capability of permitting life in complete absence of insulin. Here, I will touch upon these neuronal mechanisms and also discuss unpublished results from experiments aimed at identifying peripheral mediators of the remarkable pro-survival and anti-diabetic actions of leptin in insulin deficiency.

Michael N. Hall
Biozentrum, University of Basel, Switzerland
m.hall@unibas.ch

mTOR signaling in growth and metabolism

TOR (target of rapamycin) is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, and cellular energy. TOR was originally discovered in yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals. The discovery of TOR led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR is found in two structurally and functionally distinct multiprotein complexes, TORC1 and TORC2. The two TOR complexes, like TOR itself, are highly conserved. Thus, the two TOR complexes constitute an ancestral signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth, TOR plays a key role in development and aging, and is implicated in disorders such as cancer, cardiovascular disease, obesity, and diabetes.
While the role of TOR in controlling growth of single cells is relatively well understood, the challenge now is to understand the role of TOR signaling in disease and in coordinating and integrating overall body growth and metabolism in multicellular organisms. This will require elucidating the role of TOR signaling in individual tissues. Data on the role of mammalian TORC1 (mTORC1) and mTORC2 in controlling cellular processes and in specific tissues will be presented.

LLuis Fajas
Center for Integrative Genomics, University of Lausanne, Switzerland.

CDK4 signaling in growth and metabolism

Cyclin dependent kinase 4 (CDK4), when associated with a D-type cyclin, regulates cell cycle entry by promoting the G1>S transition and upregulating anabolic processes such as glucose uptake and lipid synthesis. Although the roles of CDK4 and its partner cyclins in the cell cycle and cancer progression have been extensively studied, we have previously showed that CDK4 can regulate metabolic processes indirectly, through activation of the E2F1 transcription factor. Here, we report that CDK4 promotes anaerobic glycolysis and represses fatty acid oxidation in mouse embryonic fibroblasts (MEFs) by directly targeting the AMP-activated protein kinase (AMPK). We also show that fatty acid oxidation (FAO) is specifically induced by the a2-subunit-containing AMPK complexes in the MEF model. Moreover, we report that CDK4 represses FAO through direct phosphorylation and inhibition of the AMPKa2-subunit. Consistent with this, CDK4 deletion leads to a massive increase in the use of fatty acids and a decrease in non-oxidative glucose utilization. Likewise, non-phosphorylable AMPKa2 mutants and the use of a chemical CDK4 inhibitor both increase FAO rates. This novel mechanism contributes to the understanding of how CDK4 translates anabolic stimuli into ATP-consuming processes, such as proliferation, by blocking AMPK promoted catabolic processes, such as FAO.

Christian Wolfrum
Department of Health Sciences and Technology, ETH Zürich, Switzerland.

Brown and brite fat - how do they contribute to metabolic control

Obesity which is associated with numerous metabolic co-morbidities is defined by an expansion of adipose tissue mass. In recent years, however it has become evident that not only the mass, but also the quality of adipose tissue plays an important role in maintaining metabolic homeostasis. Thus, adipose tissue can be subdivided into two distinct types, namely white and brown fat. While white fat is specialized in the storage of lipids, brown fat, in contrast, releases energy in the form of heat through uncoupling, leading to an enhanced basal energy expenditure. Therefore, brown adipose tissue has received tremendous interest in recent years as a target organ to improve systemic metabolic control. Currently, it remains controversial, which metabolic parameters are mainly affected by brown fat function and how much brown fat contributes to weight loss under obesogenic conditions. We have recently developed a model which allows for ablation of brown adipose tissue in adult animals and we have used this model to study the contribution of BAT to basal energy expenditure as well as to glucose and lipid homeostasis in various genetic and pharmacological paradigms. Furthermore, we could show that brown adipose tissue activity is regulated by epigenetic mechanisms, thus linking environmental cues and BAT activity. Based on our data we conclude that brown adipose tissue can be utilized to control lipid and glucose homeostasis.

Jean-Claude Martinou
Department of Cell Biology, Faculty of Sciences, University of Geneva, Switzerland

The mitochondrial pyruvate carrier in neurons and cancer cells: to carry or not to carry?

Mitochondria play a key role in energy metabolism, hosting the machinery for oxidative phosphorylation, the most efficient cellular pathway for generating ATP. A major checkpoint in this process is the transport of pyruvate produced by cytosolic glycolysis into the mitochondrial matrix, which is accomplished by the recently identified mitochondrial pyruvate carrier (MPC). As the gatekeeper for pyruvate entry into mitochondria, the MPC is thought to be of fundamental importance in establishing the metabolic programming of a cell. In this talk, I will discuss the role of the MPC in the metabolism of cancer cells and of neurons.

ABSTRACTS SUBMITTED

Knobloch Marlen
Department of Physiology, University of Lausanne

A fatty acid oxidation-dependent metabolic shift regulates adult neural stem cell quiescence

Authors list: Marlen Knobloch, Gregor-Alexander Pilz, Bart Ghesquière, Werner J. Kovacs, Thomas Wegleiter, Darcie L. Moore, Martina Hruzova, Nicola Zamboni, Peter Carmeliet, Sebastian Jessberger

Abstract: Neural stem/progenitor cells (NSPCs) generate new neurons throughout life in distinct regions of the mammalian brain. Adult neurogenesis is important for tissue homeostasis and physiological brain function, and disturbed neurogenesis has been associated with diseases such as major depression and epilepsy. A tight regulation of NSPC quiescence and proliferation is crucial to ensure life-long neurogenesis and prevent exhaustion or uncontrolled growth of the stem cell pool. What regulates this delicate balance is not fully understood. Here we show that the rate of lipid breakdown via fatty acid oxidation (FAO) defines quiescence vs. proliferation in NSPCs. Quiescent NSPCs show high expression of the key enzymes regulating FAO, such as for instance carnitine palmitoyltransferase 1a (Cpt1a). Pharmacological inhibition and conditional deletion of Cpt1a in vitro and in vivo leads to altered NSPC behavior, reducing stem cell maintenance and proper neurogenesis. Strikingly, experimental manipulation of a single metabolite that regulates levels of FAO, is sufficient to induce exit from quiescence and to enhance NSPC proliferation. Thus, the data presented here define a metabolically controlled mechanism of quiescence behavior and reveal an instructive role for fatty acid metabolism in regulating NSPC activity.

Lemos Vera
UP-Schoonjans EPFL

A SUMO-dependent LRH-1/OSBP pathway promoting nonalcoholic fatty liver disease

Authors list: Vera Lemos, Sokrates Stein, Pan Xu, Hadrien Demagny, Xu Wang, Dongryeol Ryu, Veronica Jimenez, Fatima Bosch, Thomas F. Lüscher, Maaike H. Oosterveer, Kristina Schoonjans

Abstract: Hepatic steatosis is caused by metabolic imbalances that could be explained in part by an increase in de novo lipogenesis that results from increased sterol element binding protein 1 (SREBP-1) activity. The nuclear receptor liver receptor homolog 1 (LRH-1) is an important regulator of intermediary metabolism in the liver, but its role in regulating lipogenesis is not well understood. Here, we have assessed the contribution of LRH-1 SUMOylation to the development of nonalcoholic fatty liver disease (NAFLD). Mice expressing a SUMOylation-defective mutant of LRH-1 (LRH-1 K289R mice) developed NAFLD and early signs of nonalcoholic steatohepatitis (NASH) when challenged with a lipogenic, high-fat, high-sucrose diet. Moreover, we observed that the LRH-1 K289R mutation induced the expression of oxysterol binding protein-like 3 (OSBPL3), enhanced SREBP-1 processing, and promoted de novo lipogenesis. Mechanistically, we demonstrated that ectopic expression of OSBPL3 facilitates SREBP-1 processing in WT mice, while silencing hepatic Osbpl3 reverses the lipogenic phenotype of LRH-1 K289R mice. These findings suggest that compromised SUMOylation of LRH-1 promotes the development of NAFLD under lipogenic conditions through regulation of OSBPL3.

Nasrallah Anita
CIG - UNIL

The Role of Novel Kinases in Adipose Tissue Biology

Anita Nasrallah, Isabel Lopez Mejia, Albert Giralt Coll, Sonia Vernandez-Veledo, Miriam Ejarque, Alessia Spirli, Olivier Staub, Francisco Jose Tinahones, Joan Vendrell, Lluis Fajas Coll

Abstract: It is well established that pro-inflamatory cytokines, such as IL-6 and TNF-α, affect insulin signalling, which in turn is essential to maintain glucose homeostasis and to regulate its metabolism in the liver, muscle, and adipose tissues. This leads to the stimulation of downstream protein kinases, thus activating and crosslinking numerous pathways, potentially resulting in insulin resistance. Consequently, insulin resistance status is determined by the type of activated inflammatory pathways, abnormalities of lipid metabolism, as well as in the type of activated kinases and their downstream targets. (37) The second part of our project revolves around the role of novel kinases in SAT and VAT of patients that are insulin resistant (IR) or insulin sensitive (IS). Several of the known protein kinases involved in the onset of insulin resistant are AMP-activated protein kinase (AMPK), IκB kinase (IKK), protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), etc. (38) Identifying new and specific protein kinases involved in obesity-induced chronic inflammation may help in developing the targeted drug therapies to minimize insulin resistance in patients.

Geller Sarah
Department Physiology, Unil

Production of FGF21 by hypothalamic tanycytes is modulated under fasting conditions by palmitate via a p38 MAPK signaling pathway

Authors list: Sarah Geller and Luc Pellerin

Abstract: FGF21 is an endocrine hormone produced by several peripheral organs and it plays an important role in the regulation of energy metabolism. Previous reports was shown that FGF21, which expression is enhanced in the liver under starving conditions, acts in the brain and stimulates the hypothalamic-pituitary-adrenal axis to maintain glucose homeostasis but also influenced the hypothalamic-pituitary-gonadal axis in female mice, resulting in infertility. We hypothesized that FGF21 could be also produced within the hypothalamus and could be regulated by metabolic factors to play a key role in these phenotypes. Our study shows, in adult male mouse, that hypothalamic glial cells named tanycytes, expresses and produce FGF21 in vivo and in vitro. Because it is known that tanycytes are affected by fasting conditions and could be also important sensors to detect hypoglycaemia, we have studied the effect of fasting on hypothalamic FGF21 expression. We observed a significant effect of starvation on Fgf21 expression in the hypothalamus which is restored after refeeding. Free fatty acids (FFA) are known to be elevated in fasting conditions and their uptake by the brain was positively associated with fasting. We have studied the effect of the saturated FA palmitate and the unsaturated FA oleate on Fgf21 expression in tanycytes. Only palmitate stimulate Fgf21 expression in tanycytes cultures, in the hypothalamus in vivo and an activation of p38 MAPK in tanycytes. The level of expression of Fgf21 is restored after adding the inhibitor of p38 MAPK in the culture medium. Knowing the role of FGF21 in the hypothalamus, this study suggests that Fgf21-expressing tanycytes could be pivotal elements between the metabolic status of the animal and the regulation of these physiological functions.

Shimobayashi Mitsugu
Biozentrum, University of Basel

Insulin resistance promotes inflammation in adipose tissue

Authors list: Mitsugu Shimobayashi, Verena Albert, Ralph Peterli, Bettina Woelnerhanssen, Irina Frei, Diana Weissenberger, Nicolas Clement, Suzette Moes, Marco Colombi, Jerome Meier, Marta M. Swierczynska, Paul Jenö, Christoph Beglinger, and Michael N. Hall.

Abstract: Obesity is a major risk factor for insulin resistance and type 2 diabetes. Obesity correlates with accumulation of pro-inflammatory macrophages in adipose tissue. Macrophages in adipose tissue are in turn associated with local and systemic insulin resistance. However, the causality of these events is unclear. Time course analysis during diet-induced obesity in mice showed that obesity induces insulin resistance in adipose tissue prior to accumulation of macrophages. Using insulin resistant mouse models, we demonstrate that insulin resistance in adipocytes leads to production of chemokines which recruit pro-inflammatory macrophages to adipose tissue. Together, our data suggests that insulin resistance is a cause of adipose tissue macrophage accumulation.

Honglei Ji
CIG, UNIL

Role of Cyclin Dependent Kinase 7 in adipose tissue metabolism.

Authors list: Honglei Ji, Pierre-Damien Denechaud, Isabel C. Lopez-Mejia, Judit Castillo Armengol, Lluis Fajas Coll

Abstract: Cyclin-dependent kinase 7 (CDK7) is a member of the cyclin-dependent protein kinase (CDK) family, which are important regulators of cell cycle progression and more recently, metabolism. In our project, we generated adipose tissue specific CDK7 knockout (CDK7-atKO) mice by crossing CDK7 floxed mice with ap2-cre mice. After the validation of CDK7 specific invalidation in adipose tissue, we aimed to characterize the metabolic phenotype of these mice. We found that CDK7-atKO mice have decreased body weight and fat mass compared with control mice. In vitro culture of SVF cells from subcutaneous WAT has impaired differentiation capacity, which is consistent with our in vivo data. These mice did not exhibit insulin or glucose intolerance. We did indirect calorimetry to measure energy expenditure however without difference between groups. We also found BAT of knockout mice are smaller and more “white”, which indicated an impaired BAT function. Therefore we challenged these mice with cold exposure, there is no difference in response to cold under normal condition (with food supply). However, interestingly, if food is deprived during cold exposure, the knockout mice cannot maintain their body temperature. In parallel, we detected decreased p-HSL in white adipose tissue of knockout mice, which means decreased lipolysis in WAT. So here we hypothesize that the brown adipose tissue from knockout mice cannot utilize fatty acid or do not have enough FFA supply from WAT for thermogenesis. We are still trying to validate our hypothesize and finally we aim to identify new targets of CDK7 and the signaling pathways that drive its activity in adipose tissue, which will help deepen our understanding in combating obesity and diabetes.

Castillo Armengol Judit
CIG - UNIL

CDK4, a new player in brown adipose tissue biology and adipose stem cell fate

Authors list: Judit Castillo Armengol, Isabel Lopez Mejia, Honglei Ji, Sylviane Lagarrigue, Lluis Fajas Coll

Abstract: White adipose tissue is known for its role in fat storage and whole body lipid/energy homeostasis. On the other hand, brown adipose tissue generates heat through the activity of uncoupling protein 1 (UCP1). More recently, attention has been placed into a third category of specialized heat-producing adipocytes, that can not only store lipids, but also prevent the onset of the metabolic phenoytpe. These adipocytes have been named brite (brown-in-white) adipocytes. The fact that the activities of brown and brite fat cells can limit metabolic diseases in mice, and correlate with leanness in humans underlines the importance of research in this recent field. Numerous genes and pathways that regulate brown and beige adipocyte biology have now been identified, however the role of cell cycle regulators in the development and the function of these oxidative adipose depots has not been thoroughly studied yet. We now aim to determine the role of the CDK4 in the function and differentiation of brown and brite adipocytes. Preliminary data suggests that CDK4 activity is inversely correlated with oxidative function in brown adipose tissue (BAT) and with browning in subcutaneous adipose tissue (scWAT). lndeed both morphological and gene expression data show that mice lacking CDK4 exhibit decreased lipid content and increased brown and oxidative gene expression in BAT. Under chow diet, these animals also display browning and increased oxidative gene expression in scWAT. Our preliminary data strengthen the need to study the molecular mechanisms by which CDK4 controls energy metabolism in brown and brite adipose cells. A better understanding of those processes might open up new therapeutic perspectives in the control of metabolic diseases such as diabetes or obesity.

Ivanisevic Julijana
Metabolomics Unit, Unil

Altered brain energy metabolism in Alzheimer disease: Linking peripheral and central metabolic alterations

Authors list: Tony Teav, Florence Mehl, Héctor Gallart-Ayala, Aikaterini Oikonomidi, Gwendoline Peyratout, Hugues Henry, Julijana Ivanisevic* and Julius Popp* (*Equal contribution, corresponding authors)

Abstract: The evolutionary emergence of unique cognitive skills in humans is associated with elevated metabolic gene expression and specific brain metabolic activities that are highly sensitive to changes in energy homeostasis. Neurodegenerative disorders, like Alzheimer disease (AD), are thought to be associated with alterations in central energy metabolic pathways. However, these metabolic alterations, beyond the reduced glucose metabolism, remain largely unexplored. Metabolomics, as a powerful phenotyping approach, in combination with orthogonal clinical approaches, has the potential to accelerate the understanding of mechanisms that underlie complex diseases such as AD. Here the untargeted UPLC-HRMS-based metabolomic profiling was combined with targeted quantification to unravel the metabolic signatures associated with AD. The approach was applied to peripheral blood plasma and CSF of cognitively impaired subjects with AD pathology confirmed by CSF biomarkers and healthy aged controls without cerebral AD pathology (N=72). Preliminary results suggest the distinctive metabolic phenotypes of plasma and CSF, outlining significant alterations in specific pathways. Plasma profiles mirror the downregulated lysine degradation and carnitine synthesis with the implication on fatty acid oxidation, while CSF profiles emphasize the upregulated glycine and purine metabolism. Revealed alterations at the metabolite and pathway level are being correlated with CSF markers (Aβ1, tau, and P-tau), patient's gender, BMI and blood-brain-barrier permeability. The association of peripheral metabolic changes with central metabolism and clinical meta-data will allow for the identification of metabolic biomarker signatures of AD pathology and understanding of their impact on the clinical manifestation.

Valera Alberni Miriam
NIHS

Regulation of Drp1 phosphorylation in response to metabolic and stress challenges

Authors list: Miriam Valera-Alberni, Magali Joffraud, Joanna Ratajczak, Carles Canto

Abstract: Mitochondrial connectivity is controlled by events of fusion and fission of their membranes, which regulate their morphology. Acute mitochondrial fission events are generally mediated by the recruitment of Drp1, a dynamin-related GTPase, to the mitochondrial outer membrane. This recruitment of Drp1 to mitochondria will depend mainly on the phosphorylation landscape on Ser616 and Ser637. In vitro assays have established that phosphorylation of Ser616 leads to increased Drp1 GTPase activity and mitochondrial fission, while phosphorylation of Ser637 sequesters Drp1 in the cytosol, leading to mitochondrial fusion and elongation. We have evaluated how the Ser616/ Ser637 phosphorylations are regulated in response to metabolic and stress challenges. A fasting/refeeding challenge was used to evaluate Drp1 phosphorylation changes in response to nutritional stress. We also used cold exposure as a stress challenge. Interestingly, our results illustrate that Drp1 phosphorylation response to metabolic challenges is tissue-specific. Similarly, while Ser616 and Ser637 phosphorylation antagonize each other in vitro, in vivo they can coexist simultaneously. These results open the door for novel layers of understanding about the regulation of Drp1 activity in the cell and mitochondrial morphology changes in response to environmental challenges. Further research will explore how Drp1 phosphorylation influences the metabolic adaptations required for transformation and metastatic processes.

Groeneveld Svenja
ISREC-EPFL

A mouse model to study metabolic alterations in non-small cell lung cancer.

Authors list: Svenja Groeneveld Alessandra Piersigilli Nadine Zangger Julien Faget Etienne Meylan

Abstract: During epithelial-to-mesenchymal transition (EMT), the metabolism of a cancer cell changes, likely to meet the environmental challenges faced during the metastatic process. We recently reported that the glucose transporter GLUT3 is upregulated during EMT in non-small cell lung cancer (NSCLC). Furthermore, we found that Glutamine-Fructose-6-Phosphate Transaminase 2 (GFPT2), the rate-limiting enzyme of the hexosamine biosynthesis pathway (HBP), which produces a substrate for protein modifications, is correlated with GLUT3 and upregulated during EMT as well. To investigate the metabolic alterations accompanying the EMT process in vivo, we used a genetically engineered K-ras(LSL-G12D/+);p53(fl/fl) lung tumor model and overexpressed or silenced the EMT-inducing transcription factor Snail in the lung tumor cells. Comprehensive characterization of the resulting tumors, including histological and gene expression analysis, revealed that while Snail overexpression enhanced malignant progression, it was not sufficient to result in an overt EMT phenotype. In line with this, no changes in GLUT3 or GFPT2 expression occurred upon Snail overexpression. Interestingly, gene expression and flow cytometry analyses demonstrated a strong alteration of the intratumoral immune compartment in response to Snail overexpression. Furthermore, by integrating both Snail overexpression and silencing approaches we found that Snail repressed the imprinted Dlk1-Dio3 locus, which contains one of the genome's largest cluster of miRNAs. We conclude that in our mouse model of NSCLC, chronic Snail expression is not sufficient to trigger an EMT. However, Snail exerted several functions beyond its classical role as EMT inducer, which include a previously undescribed role in regulating the Dlk1-Dio3 locus.

Li Lingzi
Department of Cellular Physiology and Metabolism, UNIGE

Identification of metabolic biomarkers for early beta-cell death in pre-diabetic mice

Authors list: Lingzi Li1, Petra Krznar2, Andrea Agazzi3, Juliette Martin-Levilain1, Sachin Supale1, Nicola Zamboni2, Pierre Maechler1 1 PHYM Department, CMU, UNIGE 2 Institute of Molecular Systems Biology, ETH Zurich 3 Theoretical Physics Department, UNIGE

Abstract: Early diagnosis of beta-cell failure remains unsuccessful despite its crucial importance in the diabetes prevention. In recent years, metabolomics emerged as a powerful tool in providing read-outs of early perturbations in diseases. Liver and plasma were collected from male db/db mice aged 4, 6 and 8 weeks, and age-matched heterozygous db/+ controls. Same collection was also done from male beta-Phb2-/- mice aged 4, 5 and 6 weeks and age-matched control mice. Metabolite profiling was performed by non-targeted FIA-TOF-MS, complemented by targeted LC-MS and GC-MS. At the age of 8 weeks and 6 weeks, respectively, db/db mice and beta-Phb2-/- mice began to display hyperglycaemia. Before the appearance of diabetes, both db/db mice and beta-Phb2-/- mice had a transient expansion of beta-cell mass, along with decreased GSIS from isolated islets. This was followed by the progressive loss of beta-cells and development of hyperglycaemia a few weeks later. However, unlike db/db mice with marked body weight gain during the pre-diabetic stage, beta-Phb2-/- mice maintained the same body weights as their age-matched controls. In the liver, cortisol increased in db/db mice during pre-diabetes, not in beta-Phb2-/- mice. Branched-chain amino acids (BCAA) increased in the liver of db/db mice, while they slightly decreased in beta-Phb2-/- mice, showing the association of BCAA with obesity and insulin resistance rather than with beta-cell dysfunction. Importantly, a specific group of deoxy sugars decreased in liver and plasma of the two mouse models at the pre-diabetic stage, showing strong correlation with the development of early asymptomatic beta-cell failure before the appearance of hyperglycaemia.

Sorrentino Vincenzo
LISP, EPFL

Enhancing mitochondrial proteostasis reduces amyloid-β peptide proteotoxicity

Vincenzo Sorrentino, Mario Romani, Laurent Mouchiroud, John S. Beck, Hongbo Zhang, Davide D'Amico, Pedro Moral Quiros, Solène Rietsch, Scott E. Counts, Johan Auwerx.

Abstract: Amyloid-β peptide (Aβ) diseases, typified by Alzheimer's disease (AD) and inclusion body myopathy (IBM), are common and devastating, yet we know relatively little about their underlying molecular mechanisms or how to treat them effectively. Here, we provide evidence of a mitochondrial stress response signature that is conserved in AD in human, mouse and C. elegans, and that involves the UPRmt and mitophagy pathways. Using a worm model of Aβ proteotoxicity, the GMC101 strain, we recapitulated mitochondrial features and confirmed the induction of this mitochondrial stress response as key to maintain mitochondrial proteostasis and health. Importantly, boosting mitochondrial proteostasis by pharmacologically and genetically targeting mitochondrial translation, biogenesis, and mitophagy increases fitness and lifespan of GMC101 worms and reduces the levels of Aβ aggregation. Our data support the relevance of enhancing mitochondrial proteostasis to delay Aβ proteotoxic diseases, such as AD and IBM.

Remacle Noémie
CHUV

New in vitro model derived from brain conditional Mut-/- mice confirms cerebral ammonium accumulation in methylmalonic aciduria

Authors list: Noémie Remacle, Patrick Forny, Hong-Phuc Cudré-Cung, Sonia Do Vale Perreira, Hugues Henry, Olivier Braissant, Matthias Baumgartner, Diana Ballhausen.

Abstract: Methylmalonic aciduria (MMAuria) is an inborn error of metabolism characterized by accumulation of methylmalonate (MMA), propionate and 2-methylcitrate (2-MCA) in body fluids. Early diagnosis and current treatment strategies are only partially effective in preventing neurological damage. We previously obtained interesting results on 3D organotypic brain cell cultures from wild-type (WT) rat embryos challenged with 2-MCA. In order to create an in vitro model which is closer to in vivo conditions, we now used 3D organotypic brain cell cultures derived from brain conditional knock-out (KO) Mut-/- mouse embryos. We tried to mimic an acute metabolic crisis by induction of a catabolic stress (fever). Metabolomics analyses in brain cell aggregates and immunohistological studies of cell morphology were performed. In accordance to our preceding findings in the WT rat model we found an important ammonium accumulation, an increase of the apoptosis rate and the suffering of neurons (cell bodies) and oligodendrocytes (signal loss). We found a decrease of glutamate dehydrogenase protein expression by western-blot. Metabolomics analyses revealed an increased MMA and acylcarnithine C3 concentration. Luminex analysis revealed altered expression levels of different chemokines. Our first results on this new model confirmed cerebral ammonium accumulation, increased apoptosis and suffering of different brain cell types. Further investigations on pathways of brain ammonium production are ongoing to understand the mechanisms leading to this accumulation. Here we show for the first time that brain cells are capable to produce significant amounts of MMA. We further demonstrate that chemokines are activated thus indicating that neuroinflammation plays a role in the neuropathogenesis of MMAuria.

Verdeguer Francisco
University of Zurich

Identification of Yin Yang 1 post-translational modifications in response to brown adipose tissue thermogenesis.

Authors list: Monika Fey, Francisco Verdeguer

Abstract: The balance of energetic metabolism is a complex regulatory system that is largely orchestrated by transcriptional and chromatin factors that cross talk with cellular and endocrine regulatory mechanisms in order to ensure a balance between energy intake and energy expenditure. Perturbations of this delicate balance can lead to obesity, a current world wide epidemic affecting 11% of population that could reach 1 billion people by 2030 (World Health Organization). Recent advances indicate that activation of brown adipose tissue thermogenesis could be an attractive therapeutic approach to elevate of energy consumption rate. We have recently shown that the loss of the transcription factor Ying Yang 1 in brown adipose tissue protects against diet-induced obesity through elevation of energy expenditure. How the excess of dietary nutrients or energy related environmental stimuli modulate the chromatin and epigenetic landscape is not completely understood. Our preliminary data show that YY1 is acetylated and dephosphorylated in response to increased adrenergic input. We hypothesize that YY1-specific post-translational modifications and the recruitment of specific chromatin factors could play a sensing role of environmental stimuli to coordinate a thermogenic response in brown adipose tissue. At present we are investigating the molecular function and physiological relevance of the YY1 post-translational modifications which could lead to a better understanding of the molecular basis of the metabolic control in physiological and pathological conditions.

Campos Vasco
EPFL - IBI

Small molecule screen for inhibitors of adipogenesis as a strategy to accelerate hematopoietic recovery

Authors list: Vasco Campos, Benjamin Rappaz, Josefine Tratwal, Yannick Yersin, Stephan Isringhausen, Cesar Nombela-Arrieta, Gerardo Turcatti, Olaia Naveiras

Abstract: Bone marrow (BM) adipocytes are the most abundant cell type in the human BM and have been recently implicated in a variety of metabolic, hormonal and physiological functions. They differ from extramedullary adipocytes in their capacity to react to the organisms' hematopoietic needs. Preventing BM adipocyte formation immediately after hematopoietic stem and progenitor cell (HSPC) transplantation has been demonstrated to accelerate engraftment and subsequent hematopoietic recovery in mice. Reducing the time of engraftment is critical to increasing the chance of survival in patients undergoing HSC transplantation. In order to uncover novel modifiers of BM adipocyte differentiation, we performed a high-throughput label-free in vitro screening on the BM-derived mesenchymal stromal cell (MSC) line, OP9. This cell line was demonstrated to be both a useful model to efficiently differentiate into adipocytes as well as to support hematopoiesis in vitro. Using Digital Holographic Microscopy (DHM), we screened the Prestwick library of FDA-approved drugs; the Swiss Chemical and natural compound collections for inhibitors of adipocytic differentiation based on real-time lipid accumulation. From the initial more than 4000 compounds around 1% rendered as hits that inhibited OP9 adipocytic differentiation. These compounds were also non-toxic to the stroma, did not affect cell number and had a strong potency (EC50<1uM). From these compounds, 15 were permissive for primary murine HSPC expansion and are currently being tested in primary HSPC/MSC co-cultures and in murine HSC transplantation. All current clinical approaches to enhance hematopoiesis target the HSC itself. Here we propose targeting BM adipogenesis as an alternative pharmacological strategy to improving hematopoietic recovery.

Brenachot Xavier
University of Geneva/PHYME

Hepatic Protein Tyrosine Phosphatase Receptor Gamma links obesity-induced inflammation to type 2 diabetes

Authors list: Xavier Brenachot, Giorgio Ramadori and Roberto Coppari

Abstract: Obesity-induced inflammation engenders insulin resistance and type 2 diabetes mellitus (T2DM). Yet, the inflammatory effector(s) linking obesity to insulin resistance is unknown. Here we show that hepatic expression of Protein Tyrosine Phosphatase Receptor Gamma (PTPR-γ) is stimulated by inflammation in obese/T2DM mice and positively correlates with indices of inflammation and insulin resistance in humans. NF-κB binds to Ptprg promoter and is required for inflammation-induced PTPR-γ expression. PTPR-γ loss-of function lowers glycemia and insulinemia and protects from development of T2DM by enhancing insulin-stimulated suppression of endogenous glucose production. These phenotypes are rescued by re-expression of Ptprg only in liver of mice otherwise lacking Ptprg globally. Importantly, hepatic PTPR-γ overexpression at level similar to the one seen in obesity is sufficient to cause severe hepatic and systemic insulin resistance. These data establish hepatic PTPR-γ as a major link between obesity and insulin resistance and unveil a new target for treatment of T2DM.

Gomes Diana
Dpt of Pathology and Immunology, University of Geneva

Insulin resistance in hepatitis C virus infection: relative contribution from liver vs. extrahepatic sites.

Authors list: D. Gomes1,*, G. Gastaldi2,*, P. Schneiter3, L. Tappy3, S. Clément4, and F. Negro4,5 1Pathology and Immunology Dpt, UNIGE; 2Division of Endocrinology, 4Clinical Pathology, and 5Gastroenterology and Hepatology, HUG; 3Physiology Dpt, UNIL

Abstract: Chronic hepatitis C (CHC) has been associated with the development of metabolic disorders, such as insulin resistance (IR). Albeit hepatitis C virus (HCV) infects only hepatocytes, peripheral IR is also observed in HCV infected patients. In the present study, we are interested to (1) identify the putative liver-derived inducers of IR in extrahepatic tissues (i.e. muscle and adipose tissue), and (2) elucidate the underlying molecular mechanisms. CHC genotype 3a patients were treated with an interferon-free regimen (ledipasvir/sofosbuvir combined with ribavirin). These patients underwent a 2-step euglycemic hyperinsulinemic clamp with tracers, together with indirect calorimetry measurement, to measure IR at start and after 6 weeks of antiviral therapy. Blood and adipose and muscle tissue biopsy samples were collected at the same time points. In vitro, human primary adipocytes were treated with the collected sera. Insulin signaling and lipid/glucose metabolism were investigated by immunoblot and RT-PCR. Insulin-stimulated glucose uptake was assessed by incubating cells with [1,2-3H(N)]-2-deoxy-D-glucose. To date, six patients have been enrolled in the clinical study, and all exhibited a significant improvement of the peripheral insulin sensitivity after successful response to treatment (p=0.0004), whereas no difference was observed in insulin-mediated lipolysis suppression. Treatment of adipocytes with sera from virally-suppressed patients increased the insulin ability to promote glucose uptake and to induce Akt phosphorylation compared to exposure to sera collected before treatment. No difference in the expression of lipid metabolism genes was observed. Taken together, these data indicate that HCV clearance might result into an improved peripheral insulin sensitivity.

Romani Mario
EPFL SV IBI-SV NCEM

Enhancing mitochondrial proteostasis reduces amyloid aggregates proteotoxicity

Authors list: Mario Romani, Vincenzo Sorrentino, Laurent Mouchiroud, John S. Beck, Hongbo Zhang, Davide D'Amico, Pedro Moral Quiros, Solène Rietsch, Scott E. Counts, Johan Auwerx.

Abstract: Aging is often accompanied by the onset of proteotoxic neuromuscular degenerative diseases, characterized by the accumulation of unfolded and aggregated amyloid proteins, such as Alzheimer disease (AD) and inclusion body myositis (IBM). To date, no efficient therapy is available to treat these diseases. However, mitochondrial dysfunction has emerged as a common hallmark of AD and IBM. Here we demostrated, using a transgenic mouse model of AD, the induction of a mitochondrial stress response that involves the UPRmt, mitophagy and Oxphos pathways. Moreover, using a human neuroblastoma cell model of amyloid disease expressing the APP Swedish K670N/M671L double mutation (APPSwe), and a mouse model of natural aging, we tested different pharmacological approaches aimed at modulating mitochondrial activity, such as NAD+ boosting and impairment of mitochondrial translation, in order to assess the potential impact on proteostasis. Using the NAD+ booster nicotinamide riboside (NR) and mitochondrial translation inhibitor Doxycycline (Dox), we achieved a reduction of the amyloid aggregates in the cell model and in the muscles of the aged mice via mitophagy and the UPRmt, and a concurrent induction of the mitochondrial stress response pathways. Together, these data identify the link between mitochondrial quality control and aggregate diseases underlying the importance of these organelles in fighting proteotoxic stress provided by the aggregation of misfolded proteins. Moreover, our data suggest a new strategy to reduce misfolded protein aggregation through the boosting of the mitochondrial activity, with potential clinical benefits in the context of degenerative disorders.