

Mini-Symposium

"Adipose tissue metabolism and cardiovascular diseases"

Organizer: Francisco Verdeguer, Department of Molecular Mechanisms of Disease,
University of Zurich

When: October 19, 2020 from 9:00 – 12:30

Where: CHUV Lausanne, main building BH08, Auditorium Auguste Tissot

PROGRAM

9:00 - 9:15	Welcome Francisco Verdeguer, Department of Molecular Mechanisms of Disease, University of Zurich
9:15 - 10:00 <i>On-site talk</i>	<u>Isabel Lopez-Mejía</u> (Center for Integrative Genomics, University of Lausanne, Switzerland) The SR protein Srsf2 modulates lipid metabolism in white adipose tissue
10:00 - 10:45 <i>On-line talk</i>	<u>Jose Javier Fuster</u> (Centro Nacional de Investigaciones Cardiovasculares Carlos III. Madrid, Spain) Somatic mutations and clonal hematopoiesis in age-related cardiovascular and metabolic disease
10:45 – 11:00	(Virtual) Coffee break
11.00 – 11:45 <i>On-line talk</i>	<u>Patrick C.N. Rensen</u> (Leiden University Medical Center, The Netherlands) Brown adipose tissue in lipid and glucose metabolism in health and disease
11:45 - 12.30 <i>On-site talk</i>	<u>Francisco Verdeguer</u> (Department of Molecular Mechanisms of Disease, University of Zurich) Transcriptional and metabolic control of brown adipose tissue thermogenesis
12.30 – 14.00	Lunch break
14:00 – 16:00	Afternoon workshops for PhD students with symposium speakers

The mini-symposium has been accredited by the Direction of veterinary affairs and their inspection (DAVI), section Lausanne, as a half day of continuing education.

The meeting is free of charge, but registration necessary [here](#) prior to October 1, 2020. The UNIL-FBM doctoral school attributes 1.0 ECTS to PhD students who present a signed participation form for the mini-symposium (0.25 ECTS morning session, 0.75 ECTS afternoon session). For additional information, please contact Dr. Ulrike Toepel (Ulrike.toepel@unil.ch).

Talk abstracts



The SR protein Srsf2 modulates lipid metabolism in white adipose tissue

Isabel Lopez-Mejía (Center for Integrative Genomics, University of Lausanne, Switzerland)

Obesity and overweight constitute a global health issue concerning 25% of the world's population that is predicted to double by 2030. Obesity is a risk factor for a large number of diseases such as cardiovascular diseases and diabetes, in addition to increasing the risk for several cancer types. The alterations that accompany obesity are driven in large part by metabolic and inflammatory changes in white adipose tissue (WAT). Despite the prevalence of obesity, no genome-wide study describing alternative splicing (AS) alterations in WAT in obese insulin resistant subjects has been published.

Using cellular and mouse models we are studying the contribution of serine- and arginine-rich (SR) protein dependent splicing, to WAT function in normal and pathological conditions. First, we measured the levels of SR proteins in mice fed a control diet, or a high-fat diet (HFD) for 8 or 20 weeks. Interestingly, the expression of Srsf2 is specifically increased in visceral WAT after 20 weeks of HFD. Using *in vitro* models, we observed an important increase in Srsf2 protein levels during white adipocyte differentiation, despite a very moderate increase in gene expression. In addition, the expression Srsf2 was consistently increased upon insulin stimulation in mature white adipocytes in normal and insulin resistant conditions. To elucidate the role of Srsf2 in WAT function *in vivo* we developed Srsf2 adipose tissue-specific knockout mice (*Srsf2*ATKO). Despite a marked decrease in fat mass and higher metabolic rates, *Srsf2*ATKO mice show impaired insulin sensitivity, in both control diet and HFD. Interestingly, in control diet, *Srsf2*ATKO mice fail to show the circadian oscillations in energy source and appear to use carbohydrates as their primary energy substrate.

RNA-seq analysis of subcutaneous and visceral WAT samples from *Srsf2*^{flox/flox} and *Srsf2*ATKO mice under control and HFD shows alterations in the expression and the AS of genes involved in fatty acid metabolism. These results point towards a key role of WAT Srsf2 in the regulation of adipose lipid metabolism that may be behind the alterations in whole-body energy homeostasis observed in *Srsf2*ATKO mice.



Somatic mutations and clonal hematopoiesis in age-related cardiovascular and metabolic disease

Jose Javier Fuster (Centro Nacional de Investigaciones Cardiovasculares Carlos III. Madrid, Spain)

The accumulation of acquired mutations is an inevitable consequence of the aging process, but its pathophysiological relevance has remained largely unexplored beyond cancer. Most of these mutations have little or no functional consequences, but in a few rare instances a mutation may arise that confers a competitive advantage to a stem cell, leading to its clonal expansion. When such a mutation occurs in hematopoietic stem cells, it leads to a situation of clonal hematopoiesis, which has the potential to affect multiple tissues beyond the bone marrow, as the clonal expansion of the

mutant stem cell is extended to circulating blood cells and tissue-infiltrating immune cells. Recent genomics and experimental studies have provided support to the notion that this somatic mutation-driven clonal hematopoiesis contributes to the development of atherosclerosis and heart failure. Emerging evidence suggest that clonal hematopoiesis may also contribute to adipose tissue inflammation and insulin resistance in the context of aging and obesity. In this talk, I will review our current understanding of this emerging cardiovascular risk modifier and the mechanisms underlying its connection to the development of cardiovascular and metabolic disorders.



Brown adipose tissue in lipid and glucose metabolism in health and disease

Patrick C.N. Rensen (Leiden University Medical Center, The Netherlands)

Patrick C.N. Rensen is professor Metabolic Aspects of Vascular Disease within the division of Endocrinology of the department of Medicine at the Leiden University Medical Center (LUMC) in Leiden, The Netherlands, and guest professor at the First Affiliated Hospital of the Xi'an Jiaotong University in China. He is Established Investigator of the Dutch Heart Foundation and the current chairman of the European Lipoprotein Club (ELC). His research mainly focuses on the role of brown adipose tissue (BAT) in lipid and glucose

metabolism and on BAT activation as a strategy to combat obesity, type 2 diabetes and cardiovascular disease. His group currently investigates novel (pharmacological) tools and targets that modulate BAT activity including GPCRs, the biological clock, the gut microbiome and exercise. In addition, he searches for novel non-invasive techniques and biomarkers to quantify BAT activity, by combining BAT-targeted intervention studies in mice and humans. He currently coauthors approx. 290 publications in international peer-reviewed scientific papers (h-index 51). Initially, his research group showed that South Asians, a population characterized by dyslipidemia and prone to develop type 2 diabetes and cardiovascular disease compared to white Caucasians, have low BAT activity correlating with low energy expenditure (Lancet Diabetes & Endocrinol 2014). In search for pharmacological strategies to activate BAT, they set out to understand the physiology of BAT. Using preclinical models BAT activation was shown to enhance selective uptake of lipoprotein-triglyceride-derived fatty acids thereby generating lipoprotein remnants that are taken up by the liver (J Lipid Res 2015; Circ Res 2016). Next, his group discovered novel pharmacological targets that modulate BAT activity with respect to uptake of plasma triglyceride-derived fatty acids, both directly (Sci Transl Med 2016) and via neural control (Diabetologia 2015; Gut 2018) and showed that BAT activation improves dyslipidemia and hyperglycemia and reduces type 2 diabetes and atherosclerosis, by both reducing atherogenic lipoproteins (Nat Commun 2015) and improving HDL functionality (Nat Commun 2017). Recently, his group demonstrated that disruption of the central biological clock predisposes to adiposity by reduced sympathetic outflow to BAT (PNAS USA 2015) and aggravates atherosclerosis development (J Pineal Res 2020), and identified a strong circadian rhythm in the uptake of plasma lipids by BAT, explaining a circadian rhythm in postprandial plasma lipid responses as well as plasma lipid levels (Cell Rep 2018). Based on these collective data, his group recently started (timed) human intervention studies in prediabetic individuals from South Asian vs white Caucasians origin aimed to activate BAT activity and to improve cardiometabolic health (Metabolism 2020).



Transcriptional and metabolic control of brown adipose tissue thermogenesis

Francisco Verdeguer (Department of Molecular Mechanisms of Disease, University of Zurich)

Obesity, a worldwide epidemic, takes place when energy intake exceeds energy expenditure. Although most current pharmacological therapies target energy intake their efficacy is very limited. On the other hand, recent discoveries show that increasing energy expenditure could be an alternative way to correct the energy balance. In this respect, the activation of brown adipose tissue thermogenesis has shown to promote metabolic homeostasis through the elevation of energy expenditure in multiple murine models. Recent advances have identified active thermogenic adipocytes in human adults and this represents a novel promising strategy to combat metabolic disorders. However, the molecular and cellular mechanisms of adipocyte thermogenesis is not fully understood. Thermogenesis is mediated by a mitochondrial protein, UCP1, which dissipates the intermembrane proton gradient and uncouples the oxidative phosphorylation from ATP production. This leads to an exacerbated catabolism of nutrients including glucose and fatty acids. Adrenergic input through cAMP-mediated signalling is known to induce gene activation of the key transcriptional regulators such as PGC-1 α /PPAR γ which lead to UCP1 transcription. Whether other transcriptional or chromatin regulators control adipose tissue thermogenesis remains partially understood.

Our recent discoveries identified the transcription factor Yin Yang 1 as a key regulator of whole-body energy balance through the control of thermogenic function in adipose tissue. In addition, our recent preliminary data show that YY1 dephosphorylation at S120 induced by adrenergic signalling leads to thermogenic activation in brown adipose tissue.

We have identified CK2 as the kinase which phosphorylates YY1 at S120 and furthermore showed that CK2 inhibition leads to UCP1 increased expression. Post-translational modifications such as phosphorylation of proteins play an essential role in multiple cellular and physiological processes. The role of phosphatases in brown adipose tissue thermogenesis is unknown. We have now identified the regulatory subunit PPP1R3B as a cold induced factor in brown adipose tissue, suggesting a role in thermogenesis. We have in addition shown that PPP1R3B interacts with YY1, suggesting a role in YY1 dephosphorylation. We are currently investigating the molecular and genomic role of YY1-(S120) phosphorylation in adipose tissue. We understand the mechanisms of YY1 dephosphorylation by addressing the novel YY1-PPP1R3B signalling axis in the regulation of thermogenesis and energy balance in brown adipocytes. Our transcriptomic preliminary data suggest that YY1 phosphorylation plays a switch role between anabolism and catabolism. How YY1 phosphorylation status orchestrates opposite transcriptional programs is not known. We are in addition investigating the genomic binding of YY1 and identifying its molecular interactors at the chromatin level in function of its phosphorylation status. Altogether these questions have a strong relevance in the understanding how transcription factors, here YY1, sense environmental stimuli to regulate energetic balance. This increased knowledge would be important to identify novel routes potentially amenable for drug therapy in metabolic diseases leading to excessive energy storage.