LIMNA
Lausanne Integrative Metabolism & Nutrition Alliance

SEMINAR

Thursday March 15 , 2018 – 9h30
Conference room AI 1153 (*) - EPFL - Lausanne

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"Brown adipose tissue – new option in the therapy of metabolic disease?"

Host: Prof. Kristina Schoonjans

Abstract:
The recent "re-discovery" of brown adipose tissue (BAT) in humans is one of the most intriguing findings in the research area of metabolic diseases as it raised hope for the treatment of obesity. In addition to brown adipocytes present in BAT depots, inducible brown-like adipocytes so called beige adipocytes can be found in specific WAT depots under various catabolic conditions such as cold exposure in wintertime. Cold-activated beige and brown adipocytes trigger an energy-demanding process known as adaptive thermogenesis, which requires increased uptake of dietary carbohydrates and lipids for maintaining caloric balance. The relevance of BAT is exemplified by the fact that in rodents, BAT and liver take up equal amount of energy from the bloodstream, a process which is able to normalize glucose and lipid values in insulin resistant and hyperlipidemic mice. Notably, also in humans most of the standard metabolic parameters routinely determined by physicians such as glucose and blood lipids are influenced by brown and beige adipocyte activity.
Recently, we investigated in more detail the regulation as well as the molecular processes of lipid disposal into activated BAT, using pharmacological and genetic interventions in mice. We found that short-term BAT activation by cold exposure or beta-3-adrenergic receptor agonism triggers insulin secretion, a process depending on fatty acid release by white adipose tissue. Furthermore, we showed that both insulin release and brown adipocytes insulin sensitivity is essential for the replenishment of endogenous energy stores and efficient adaptive thermogenesis. These data demonstrate that both catabolic and anabolic processes are important for energy balance and function of BAT. In addition to increased fatty acid disposal, we found enhanced uptake of dietary cholesterol into activated BAT as consequence of lipoprotein internalization. Following the fate of cholesterol, we observed the induction of hepatic bile acid synthesis, interestingly via the alternative but not the classical pathway. This process, depending on hepatic CYP7B1 induction, results in elevated plasma levels and pronounced fecal excretion of conjugated bile acids, accompanied by distinct changes in gut microbiota. Pharmacological intervention using ezetimibe, a drug blocking dietary cholesterol uptake, prevented both the rise in bile acid excretion and compositional changes in gut bacteria in response to cold. These results identify bile acids generated in the liver as the determinant of cold-induced gut microbiota, highlighting the relevance of cholesterol metabolism by the host for diet-induced changes on gut microbiota and energy metabolism.
Altogether, our results demonstrate the functional relevance of thermogenic adipocytes for systemic energy and lipoprotein metabolism. In this light, increasing adaptive thermogenesis may represent a promising therapeutic approach for obesity-associated metabolic diseases.

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