

Functional Genomics and Metabolism

Distinguished Seminar

Tuesday, October 1 from 13.00-14.00
in BMB Seminar room (V18-501-1)

“Brown adipose tissue and systemic lipoprotein metabolism”



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Host: Prof. Jan-Wilhelm Kornfeld

Abstract

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.