UKE Paper of the Month September 2017

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Cold-induced conversion of cholesterol to bile acids in mice shapes the gut microbiome and promotes adaptive thermogenesis

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ABSTRACT: Adaptive thermogenesis is an energy-demanding process that is mediated by cold-activated beige and brown adipocytes, and it entails increased uptake of carbohydrates, as well as lipoprotein-derived triglycerides and cholesterol, into these thermogenic cells. Here we report that cold exposure in mice triggers a metabolic program that orchestrates lipoprotein processing in brown adipose tissue (BAT) and hepatic conversion of cholesterol to bile acids via the alternative synthesis pathway. This process is dependent on hepatic induction of cytochrome P450, family 7, subfamily b, polypeptide 1 (CYP7B1) and results in increased plasma levels, as well as fecal excretion, of bile acids that is accompanied by distinct changes in gut microbiota and increased heat production.
Genetic and pharmacological interventions that targeted the synthesis and biliary excretion of bile acids prevented the rise in fecal bile acid excretion, changed the bacterial composition of the gut and modulated thermogenic responses. These results identify bile acids as important metabolic effectors under conditions of sustained BAT activation and highlight the relevance of cholesterol metabolism by the host for diet-induced changes of the gut microbiota and energy metabolism.

STATEMENT:

Our work identified a novel interplay of brown adipose tissue and liver resulting in the conversion of excess cholesterol into bile acids which subsequently determine the composition of the gut bacteria. This process maintains systemic lipid homeostasis under conditions of high dietary cholesterol uptake. In addition, the bile acids generated through this mechanism exert beneficial effects on the host, probably via bioactive metabolites released by gut bacteria. Targeting this process would be a novel approach for the treatment of obesity-associated inflammatory diseases such as NASH, atherosclerosis and diabetes.

BACKGROUND:

The work was performed at the Department of Biochemistry and Molecular Cell Biology in the lab of Prof. Dr. Jörg Heeren, Heisenberg Professor of Immunometabolism. The PhD student Anna Worthmann (SFB841) and Dr. Clara John (KFO306) were the leading junior scientists on the project. This work was supported by grants funded by the DFG (SFB841, KFO306), through an EFSD award and by the EU FP7 project RESOLVE.