The role of carboxylesterase 2 members in hepatic lipid metabolism

Summary

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Supervisor:	Prof. Dr. Günter Hämmerle
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

The breakdown of TGs from cytosolic lipid droplets is a 3-step process and requires the lipolytic activity of ATGL, HSL, and monoglyceride lipase (MGL). Unexpectedly, liver-specific disruption of ATGL does neither affect hepatic lipoprotein TG production nor insulin sensitivity despite massive hepatic steatosis, whereas hepatic HSL deficiency does not affect TG homeostasis in the liver. These findings suggest that other lipases are involved in hepatic lipolysis and lipid signaling pathways. Recent studies demonstrated reduced expression or activity of carboxylesterase 2 (CES2) in the liver of non-alcoholic steatohepatitis patients (1) and in obese individuals (2), respectively. In mice, injection of recombinant adenovirus expressing human CES2 provokes a substantial down-regulation of Ces2 members that may indicate a role for Ces2 proteins in hepatic lipid catabolism. In line with such an assumption, preliminary studies in our laboratory demonstrate that Ces2 members efficiently hydrolyze TGs.

Hypothesis and Objectives:

Ces2 family members are TG hydrolases involved in hepatic lipid catabolism and signaling. We will overexpress Ces2 candidate cDNA in hepatic cell lines and in mice to study their role in liver lipid and energy metabolism.

Methodology:

We will characterize lipid hydrolytic activities of murine Ces2 members and human CES. We will generate Ces2 recombinant lentivirus for stable overexpression in murine and human liver cell lines to study the impact on cellular lipid and energy metabolism. To assess the in vivo role of selected Ces2 members in hepatic lipid metabolism, we will generate Ces2/CES2 recombinant adenovirus and examine lipid and energy homeostasis in mice upon injection of recombinant adenovirus.

References:

1. Li Y, Zalzala M, Jadhav K, Xu Y, Kasumov T, Yin L, Zhang Y. Carboxylesterase 2 Prevents Liver Steatosis by Modulating Lipolysis, ER stress and Lipogenesis and Is Regulated by HNF4α. Hepatology. 2017; 63: 1860-74
2. Ruby MA, Massart J, Hunerdosse DM, Schönke M, Correia JC, Louie SM, Ruas JL, Näslund E, Nomura DK, Zierath JR. Human Carboxylesterase 2 Reverses Obesity-Induced Diacylglycerol Accumulation and Glucose Intolerance. Cell Rep. 2017; 18: 636-46

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