Medical University of Graz

Role of human carboxylesterase 2 in liver disease development

Summary

Guenter Haemmerle, Institute of Molecular Biosciences, University of Graz

Supervisor:	Prof. Dr. Günter Hämmerle
Availability:	This position is available.
Offered by:	University of Graz
Application deadline:	Applications are accepted between August 14, 2020 00:00 and October 10, 2020 23:59 (Europe/Zurich)

Description

Background:

Mice lacking Adipose triglyceride lipase (ATGL), the limiting enzyme in cellular triglyceride (TG) catabolism, are protected from hepatic steatosis (1) suggesting that other lipases are involved in the development of non-alcoholic fatty liver disease (NAFLD). We recently demonstrated that Ces2c, a member of the murine Carboxylesterase 2 (Ces2) protein family, efficiently hydrolyzes TGs and diglycerides in hepatic cell lines and that intestine-specific Ces2c overexpression protects mice from diet induced hepatic steatosis (2). In humans, reduced hepatic expression of carboxylesterase 2 (CES2) has been linked to the development of fatty liver disease implicating that murine Ces2c can be the functional orthologe of human CES2.

Hypothesis and Objectives:

We hypothesize that human CES2 plays a critical role in hepatic lipid metabolism, lipid signaling, and the development of hepatic disorders and that murine Ces2c is the functional orthologe of human CES2. In this project we will elucidate the *in vivo* role of human and murine CES2/Ces2c in liver lipid metabolism and NAFLD development. We will address the impact of hepatocyte-specific overexpression of human CES2 on liver lipid metabolism in wildtype (WT) and Ces2c mutant mice.

Methodology:

We will generate CES2/Ces2c mutant liver cell lines and Ces2c-deficient mice applying CRISPR/Cas9 technology and lentiviral vectors. We will study the impact of CES2/Ces2c overexpression or deletion on hepatic lipid metabolism in cell culture and mice. To assess the *in vivo* role of human CES2 in liver lipid metabolism and signaling, we will stably overexpress a human CES2 transgene in the liver of WT and Ces2c mutant mice and investigate the impact on liver and whole-body lipid and energy metabolism.

References:

1. Haemmerle G, …, Zechne R. ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-alpha and PGC-1*. Nat Med. 2017; 17:1076-85.*

2. Maresch LK, …, Haemmerle G. Intestine-Specific Overexpression of Carboxylesterase 2c Protects Mice From Diet-Induced Liver Steatosis and Obesity. *Hepatol Commun.* 2018; *3:227-245.*

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