Medical University of Graz

Role of human carboxylesterase 2 in hepatic lipid metabolism

Summary

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Supervisor:	Prof. Dr. Günter Hämmerle
Availability:	This position is available.
Offered by:	University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background: Mice lacking Adipose triglyceride lipase (ATGL) are protected from high fat diet induced hepatic steatosis 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 (1). In humans, reduced hepatic expression of carboxylesterase 2 (CES2) has been linked to the development of non-alcoholic steatohepatitis (2) implicating that Ces2c can be the murine orthologe of human CES2.

Hypothesis and Objectives: We hypothesize that human CES2 plays a critical role in hepatic lipid metabolism and NAFLD development 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 lipid signaling. 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. Maresch LK, Benedikt P, Feiler U, Eder S, Zierler KA, Taschler U, Kolleritsch S, Eichmann TO, Schoiswohl G, Leopold C, Wieser BI, Lackner C, Rülicke T, van Klinken J, Kratky D, Moustafa T, Hoefler G, Haemmerle G. Intestine-Specific Overexpression of Carboxylesterase 2c Protects Mice From Diet-Induced Liver Steatosis and Obesity. *Hepatol Commun*. 2018; 3:227-245.

2. 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.

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