

Crosstalk of lysosomal lipid degradation in liver and adipose tissue

Summary

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Supervisor: Prof. Dr. Dagmar Kratky
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

Research interests and scientific background:

Fatty acids are the most efficient substrates for energy production in vertebrates and essential components of biological membranes. Release of fatty acids from triglycerides (TG) requires their enzymatic hydrolysis by a process called lipolysis. D. Kratky's group is particularly interested how cytosolic "neutral" lipolysis in lipid droplets and "acid" lipolysis in lysosomes (lipophagy) degrade cellular TG, how these pathways communicate, how they affect lipid metabolism and energy homeostasis, and how their dysfunction affects the pathogenesis of metabolic diseases (reviewed in (1)). The group generates and phenotypically characterizes transgenic as well as global and tissue-specific lipase knock-out mouse models with special emphasis on lipid and energy metabolism.

In humans and mice, deficiency of lysosomal acid lipase (LAL) mostly affects liver, intestine, and macrophages. Due to the severe phenotype of systemic Lal-deficient (-/-) mice (2,3), we aim to characterize tissue-specific Lal^{-/-} mouse models to clarify cell-specific functions and the consequences on lipid and energy metabolism.

Affiliation: Dagmar Kratky's group is located at the Gottfried Schatz Research Center, Molecular Biology and Biochemistry, Medical University of Graz. This project is part of the SFB Lipid Hydrolysis and the student will be enrolled in the DK-MCD.

Hypothesis and objective: To elucidate the cause and consequence of metabolic adaptations in Lal^{-/-} mice, we have already generated floxed mice and started to eliminate LAL in various cells and organs. We have very recently shown that hepatocyte-specific (hep)Lal^{-/-} mice exhibit a similar decrease in hepatic LAL activity as systemic Lal^{-/-} mice (4). The crosstalk between hepatocyte LAL deficiency and lipid accumulation in the liver with the inability of white adipose tissue to accumulate lipids, however, is intriguing and the underlying mechanisms are still elusive. We hypothesize that the loss of LAL in the liver affects cellular signaling and lipid/energy homeostasis by altering the expression and posttranslational modification patterns of target proteins.

Experimental approaches: The student will investigate the consequences of LAL deficiency in the liver on adipose tissue development and hepatic inflammation. To identify potential secretory factors that affect adipogenesis and adipocyte metabolism in the absence of LAL, the DK-MCD student will isolate mRNA and protein from adipocytes, hepatocytes and Kupffer cells and perform transcriptome, proteome, and phosphoproteome analyses. In isolated cells and *in vivo*, the student will determine lipid uptake and secretion, investigate glycolysis, gluconeogenesis, and inflammation, and analyze important signaling pathways that regulate adipogenesis, adipose tissue maintenance, and tissue remodeling using wild-type, systemic Lal^{-/-}, and hepLal^{-/-} mice.

Results from these experiments will help to understand the mechanism(s) of resistance to diet-induced obesity of hepLal^{-/-} mice (4). In addition, the DK-MCD student will investigate the role of the liver in the observed cold intolerance of systemic Lal^{-/-} mice (5).

References:

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3. Du H, Heur M, Duanmu M, Grabowski GA, Hui DY, Witte DP, Mishra J. Lysosomal acid lipase-deficient mice: depletion of white and brown fat, severe hepatosplenomegaly, and shortened life span. *J Lipid Res*. 2001; 42:489-500
4. Leopold C, Duta-Mare M, Sachdev V, Goeritzer M, Maresch LK, Kolb D, Reicher H, Wagner B, Stojakovic T, Ruelicke T, Haemmerle G, Hoefler G, Sattler W, Kratky D. Hepatocyte-specific lysosomal acid lipase deficiency protects mice from diet-induced obesity but promotes hepatic inflammation. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019; 1864:500-11
5. Duta-Mare M, Sachdev V, Leopold C, Kolb D, Vujic N, Korbilius M, Hofer DC, Xia W, Huber K, Auer M, Gottschalk B, Magnes C, Graier WF, Prokesch A, Radovic B, Bogner-Strauss JG, Kratky D. Lysosomal acid lipase regulates fatty acid channeling in brown adipose tissue to maintain thermogenesis. *Biochim Biophys Acta*. 2018; 1863:467-78



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