Lysosomal lipid degradation in the small intestine

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 July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich)

Description

Research interests:

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 knockout mouse models with special emphasis on lipid and energy metabolism.

Scientific background:

In humans and mice, deficiency of lysosomal acid lipase (LAL) mostly affects the liver, intestine, and macrophages, leading to accumulation of neutral lipids within fatty lysosomes. Depending on the residual activity of LAL and the severity of the disease, patients with LAL deficiency (LAL-D) die within the first months of age (Wolman disease) or survive until adulthood but with massive metabolic disturbances (cholesteryl ester storage disease). The substantial intestinal macrophage infiltration in LAL-D patients makes it difficult to determine whether enterocytes or immune cells underlie the development of the observed intestinal condition. Although the intestinal defects in LAL-D, leading to severe lipid malabsorption, may represent the major cause of death in Wolman disease patients, detailed information of the underlying etiology is scarce and limited to a small number of case reports. Knowledge of specific pathomechanisms that lead to intestinal dysfunction remains elusive. Due to the severe phenotype of systemic Lal-deficient mice (2, 3), we aim to characterize tissue-specific Lal-deficient 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. The student will be enrolled in the DK-MCD and the project will be connected to the SFB LIPID HYDROLYSIS (https://www.medunigraz.at/lipid-hydrolysis/).

Hypothesis and objective:

In the small intestine of Lal-deficient mice, we observed massive cholesteryl ester and TG accumulation in enterocytes and macrophages (unpublished). Lipid accumulation in resident macrophages of the small intestine suggests that macrophages are not solely responsible for guarding the critical points of pathogen entrance, but also interact with lipoproteins more dynamically than parenchymal cells. To elucidate the physiological roles of LAL in the small intestine, the student will use global Lal-, macrophage-specific (mac)Lal-, and intestine-specific (int)Lal-deficient mice to study enterocyte function, lipid absorption, and the involvement of enterocytes and macrophages in the severe phenotype of LAL-D. The characterization of these mutant mouse models enables a characterization of the progression of disease development from an early mild state to the severe phenotype, which is a prerequisite for understanding the cell/tissue-specific function of LAL.

Experimental approaches:

The student will investigate the consequences of LAL deficiency in the small intestine on gut transit, lipid uptake and absorption, lipid and chylomicron secretion, and lipid excretion. In particular, the DK-MCD student will determine the individual roles of macrophages and enterocytes in the intestinal pathology of LAL-D. Morphometric and histological analyses of intestinal sections of normal chow diet- and high fat/high cholesterol diet-fed mice will include hematoxylin/eosin staining to determine *e.g.* villus height, depth of the crypt, villus and connective tissue width. Oil red O, sirius red, and F4/80 staining will assess neutral lipid accumulation, collagen deposition, and macrophage infiltration.

References:

1. Zechner R, Madeo F, Kratky D. Cytosolic lipolysis and lipophagy: two sides of the same coin. *Nat Rev Mol Cell Biol*. 2017; 18:671-84
2. Radovic B, Vujic N, Leopold C, Schlager S, Goeritzer M, Patankar JV, Korbelius M, Kolb D, Reindl J, Wegscheider M, Tomin T, Birner-Gruenberger R, Schittmayer M, Groschner L, Magnes C, Diwoky C, Frank S, Steyrer E, Du H, et al. Lysosomal acid lipase regulates VLDL synthesis and insulin sensitivity in mice. *Diabetologia*. 2016; 59:1743-52
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

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