Medical University of Graz

Consequences of MMP12 loss in lysosomal acid lipase deficiency

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 10, 2020 00:00 and March 30, 2020 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 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 triglycerides, 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). Matrix metalloproteinase 12 (MMP12), a macrophage-secreted extracellular matrix protein (2), has been identified as a massively upregulated pro-inflammatory factor in patients affected by LAL-D. Validation of microarray experiments using lung tissue from Lal-deficient mice helped to identify *Mmp12* as the highest expressed gene compared to wild-type mice (3, 4). However, studies investigating the potential detrimental role of MMP12 in LAL-D are missing. Therefore, we aim to (i) understand the role of MMP12 in LAL-D (using Lal-deficient mice), (ii) investigate the effects of MMP12 in macrophage (dys)function, and (iii) elucidate the potential positive effects of MMP12 depletion in LAL-D using an immunotherapeutic strategy.

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.

Hypothesis and objective:

MMP12 is the highest upregulated gene in lungs of Lal-deficient mice (4). We observed a drastic MMP12 upregulation in several tissues and plasma of Lal-deficient mice, which augmented with the progression of the disease (unpublished data). We will therefore generate Lal/Mmp12 double knockout (DKO) mice and neutralize MMP12 in Lal-deficient mice to assess the consequences of MMP12 loss on lipid and energy metabolism. We hypothesize that (i) MMP12 contributes to the pathology of LAL-D by triggering macrophage dysfunction and that (ii) MMP12 depletion or neutralization may lead to an improvement in the pathogenesis of LAL-D.

Experimental approaches:

The student will investigate the effects of MMP12 in macrophage (dys)function and the consequences of its depletion in LAL-D in adipose tissue development and hepatic inflammation. To investigate the effects of MMP12 in macrophage

Medical University of Graz

(dys)function, the student will isolate human peripheral blood mononuclear cells from buffy coats, differentiate them into macrophages and silence *Mmp12*. Functional analyses of these cells will include: phagocytosis, efferocytosis, cell morphology and migration as well as neutral lipid accumulation and quantitation. To elucidate the consequences of MMP12 depletion in LAL-D in energy metabolism, insulin sensitivity, adipose tissue and hepatic inflammation, and atherosclerosis, the student will utilize two *in vivo* experimental approaches: 1) Lal/Mmp12-DKO mice and 2) a short-term neutralization of MMP12 in Lal-deficient mice.

Results from these experiments will provide new insights for better understanding the functions of MMP12 in LAL-D, which might eventually represent a novel therapeutic approach for the treatment of this severe disease.

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. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. *Cardiovasc Res*. 2006; 69:562-73
3. Lian X, Yan C, Yang L, Xu Y, Du H. Lysosomal acid lipase deficiency causes respiratory inflammation and destruction in the lung. *Am J Physiol - Lung Cell Moll Physiol*. 2004; 286:L801-7
4. Lian X, Yan C, Qin Y, Knox L, Li T, Du H. Neutral lipids and peroxisome proliferator-activated receptor-{gamma} control pulmonary gene expression and inflammation-triggered pathogenesis in lysosomal acid lipase knockout mice. *Am J Pathol*. 2005; 167:813-21

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