Lysosomal lipid degradation in bone and muscle development

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 knockout mouse models with special emphasis 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 is connected to the SFB Lipid Hydrolysis.

Hypothesis and objective: In one of our lipase-deficient mouse models, we observed smaller tibia length as well as increased bone friability and porosity in an age-dependent manner. Lipid metabolism was only recently connected to osteoblast differentiation and bone homeostasis (2). We hypothesize that the respective lipase is required for normal bone development and we aim to identify the underlying mechanisms.

Recent results also suggested impaired skeletal muscle function in lipase-deficient mice. Decreased skeletal muscle mass, increased muscle proteolysis markers, altered fatty acid composition, and decreased acetyl-CoA availability in skeletal muscle suggest that alterations in skeletal muscle fatty acid metabolism might be involved in the intolerance of lipase-deficient mice to cold. Altered metabolite concentrations in skeletal muscle, markedly affected glycolysis, and decreased locomotor activity in mice kept at room temperature indicate impaired muscle function and increased muscle fatigue in these mice. Thus, we hypothesize that the availability of this lipase in skeletal muscle might be involved in thermogenesis.

Experimental approaches: The DK-MCD student will utilize lipase-deficient mouse models as *in vivo* model to investigate the consequences of lipase deficiency on bone and muscle development. To elucidate whether energy supplementation (from fat and/or glucose) influences bone development and marrow adiposity, s/he will perform skeletal phenotyping using µCT scanning techniques and quantify marrow fat using combined µCT scanning and osmium tetroxide staining (3). To determine a potential cell-autonomous role of the respective lipase, the DK-MCD student will isolate bone marrow-derived stromal cells and primary calvaria osteoblasts for studying the osteoblast differentiation capacity under various culture conditions. Fluorescence microscopy after staining of tissue sections for neutral lipids, lipid droplets, and lysosomes will decipher the distribution of cellular lipid pools. Bioenergetics profiling using Seahorse experiments and lipidomics analyses will help to determine if the cells change their metabolic programming in the absence of the respective lipase. Isolated skeletal muscles will be screened for metabolites by nuclear magnetic resonance spectrometry and liquid chromatography-mass spectrometry and investigated for muscle damage, lipolysis, glycolysis, and substrate oxidation markers by real-time PCR, western blotting experiments, and biochemical analyses.

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. Rendina-Ruedy E, Guntur AR, Rosen CJ. Intracellular lipid droplets support osteoblast function. Adipocyte. 2017; 6:250-8
3. Scheller EL, Troiano N, Vanhoutan JN, Bouxsein MA, Fretz JA, Xi Y, Nelson T, Katz G, Berry R, Church CD, Doucette CR, Rodeheffer MS, Macdougald OA, Rosen CJ, Horowitz MC. Use of osmium tetroxide staining with microcomputerized tomography to visualize and quantify bone marrow adipose tissue in vivo. Methods Enzymol. 2014; 537:123-39

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