The role of human ATGL in cardiac signaling and energy metabolism

Summary

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Supervisor:	Prof. Dr. Günter Hämmerle
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

Background:

ATGL-deficiency provokes severe cardiac steatosis and heart dysfunction in humans and mice (1). Unexpectedly, however, impaired ATGL-mediated TG catabolism in cardiac muscle of Plin5 transgenic mice neither affects heart function nor life span despite massive cardiac fat accumulation (2). Residual ATGL activity and accordingly low cardiac lipolysis in patients harboring mutated *ATGL* alleles does not provoke life-threatening cardiac dysfunction suggesting that impaired TG breakdown and consequently diminished FA supply from endogenous TG deposits are not the main cause of heart dysfunction in humans carrying mutated *ATGL* alleles.

Hypothesis and Objectives:

Low ATGL-mediated cardiac lipolysis in humans and mice does not provoke lethal heart dysfunction in aged individuals and mice, respectively. These findings may suggest that ATGL exerts an actually unknown function(s) in cardiac metabolism. We aim at elucidating the role of (human) ATGL in cardiac energy metabolism beyond its established role in FA supply as energy substrate.

Methodology:

We will generate cardiac cell lines overexpressing human ATGL harboring low lipolytic activity and study the impact on PPAR signaling and FA oxidation. Further, we will study the interaction of human ATGL with the lipolytc co-activator CGI-58 or Plin5. To study the *in vivo* role of human non-mutated versus mutated ATGL in cardiac energy metabolism, we will generate transgenic mice expressing human *ATGL* cDNA under the control of the cardiac-specific α-MHC promoter. In the next step, Atgl-deficient mice solely expressing human non-mutated/mutated ATGL cDNA in cardiac muscle will be generated and cardiac lipid and energy metabolism will be examined.

References:

1. Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, Heldmaier G, Maier R, Theussl C, Eder S, Kratky D, Wagner EF, Klingenspor M, Hoefler G, Zechner R. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science*. 2006; 312: 734-7

2. Pollak NM, Jaeger D, Kolleritsch S, Zimmermann R, Zechner R, Lass A, Haemmerle G. The interplay of protein kinase A and perilipin 5 regulates cardiac lipolysis. *J Biol Chem*. 2015; 290: 1295-306

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