The role of bile acids in lipid and energy metabolism in health and disease

Summary

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Supervisor: Prof. Dr. Peter Fickert
Availability: This position has been occupied.
Offered by: Medical University of Graz
Application deadline: Applications are accepted between August 01, 2016 00:00 and September 30, 2016 23:59 (Europe/Zurich)

Description

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Research interest: The group of P. Fickert investigates the molecular mechanisms of bile acid (BA) signaling under physiological (e.g. lipid metabolism) and pathophysiological conditions as a critical regulator of liver diseases, such as cholestasis. In addition, certain BAs, such as the side chain-shortened nor-ursodeoxycholic acid (norUDCA) are also used in treatment of these disorders. This resulted in several key publications in this area of research and international patents on the clinical use of norUDCA as novel treatment for cholestatic liver diseases (Patent WO2006119803) and atherosclerosis (Patent 07 113 107.2).

Background: BAs previously seen as simple fat emulsifiers are now known to represent a major molecular regulator of lipid, glucose, and energy homeostasis, therefore currently denominated as hormones. The enterohepatic circulation of bile acids from the liver to intestine and back to the liver, describe best their primary place of action, such as control of microbiota diversity and intestine barrier function, and conversion of cholesterol, promoting their biosynthesis and biliary excretion [1, 2]. Our recent data demonstrate that certain BAs, including norUDCA counteract aberrant cellular proliferation, ER-stress and inflammation, and exert different effects on mTORC1 activation, ribosome biogenesis, and autophagy. Using microarray technology and metabolic profiling, our lab was additionally able to uncover profound changes in systemic and hepatic cholesterol, phospholipid, triglyceride and fatty acid metabolism [3]. Intriguingly, it seems that hepatic lipid metabolism is of prime importance in the pathogenesis of various liver diseases, and that “metabolic reprogramming” is essential to exert beneficial effects by BAs such as norUDCA.

Hypothesis and Objectives: The thesis will focus on the characterization of molecular and metabolic pathways through which BAs impact on hepatic and intestinal lipid and energy metabolism in health and disease.

Methodology: Within this research project the candidate will use both in vivo and in vitro models to determine the impact of BAs on steroid/lipid (patho)-physiology. In the context of the enterohepatic circulation, the student will investigate the impact of different BAs on intestine and liver metabolism using numerous mouse models, e.g. lacking the nuclear BA-receptor FXR or the G protein-coupled bile acid receptor 1 (GPBAR1). This will be further attained using a setting of different dietary manipulation e.g. high fat diet. Part of the project will also include the analysis of the microbiota environment with regard to BA-metabolism. The student will work with liver and intestinal cell lines and will perform knock-down and/or overexpression experiments to elucidate molecular mechanisms in vitro.

Consequently, the student should learn to plan experiments independently, develop own research ideas, and perform standard techniques of molecular cell biology (e.g. cloning of cDNA, Q-PCR), cell culture work, cell biology (immunohistochemistry and immunofluorescence microscopy) and protein-protein interactions by immunoprecipitation.

Laboratory environment: The DK-MCD student will work in a young and motivated laboratory of currently 6 scientifically experienced group members and 3 technicians. The laboratory is located at the Center of Medical Research (ZMF), which provides all infrastructures for this project.

Required experience: We are looking for a highly motivated PhD student, with a great passion for science, holding a master in Biology (Biochemistry/Molecular Biology/Cell Biology or similar education).

Further information: https://forschung.medunigraz.at/fodok/suchen.person_uebersicht?sprache_in=en&sicht_in=&menue_id_in=101&id_in=80264
References:


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