Lipid hydrolysis pathways in progression of cholestatic and metabolic liver disease

Summary

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Supervisor:	Prof. Dr. Michael Trauner
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:

Lipid hydrolysis products, in particular FAs, are potent signaling molecules activating intracellular stress/danger pathways and serve as endogenous ligands for nuclear receptors such as PPARs as key regulators of hepatobiliary transport, metabolism, and inflammation. These nuclear receptors have become important novel therapeutic targets in non-alcoholic fatty liver disease (NAFLD/NASH) and cholestatic liver diseases such as primary sclerosing cholangitis (PSC). Lipid degradation mediated by ATGL/PNPLA2 and its cofactor CGI-58 plays a key role in hepatic lipid homeostasis. Patients with ATGL/PNPLA2 mutations show fat accumulation in muscle tissues and heart dysfunction, while genetic variants of PNPLA3 (the closest homologue of ATGL/PNPLA2 within the PNPLA family) results in enhanced susceptibility to NAFLD/NASH and progression of other liver diseases including PSC and liver cancer. Our work is focused on the role of lipid hydrolysis pathways and nuclear receptor signaling in cholestatic and fatty liver disease. We aim to understand the cellular interplay of these pathways in different liver cell types such as hepatocytes, cholangiocytes (bile duct epithelial cells), Kupffer cells (liver tissue resident macrophages), and fibrogenic hepatic stellate cells (HSCs) in the pathogenesis and progression of liver diseases that eventually lead to fibrosis, cirrhosis and cancer.

Affiliation:

The PhD student will work at the Hans Popper Laboratory of Molecular Hepatology of the Medical University of Vienna. This project is connected to the SFB Lipid Hydrolysis.

Hypothesis and objective:

We hypothesize that dysregulated lipid hydrolysis and lipid signaling pathways play a critical role in the progression of chronic liver injury by determining pro-inflammatory and pro-fibrogenic molecular features of cholangiocytes and macrophages/Kupffer cells in addition to metabolic changes in hepatocytes. Our overall goal is to explore the liver cell-specific role and multicellular interplay of lipid hydrolysis pathways (ATGL/PNPLA2, its co-regulator CGI-58, and PNPLA3) underlying the progression of metabolic and cholestatic liver diseases toward inflammation, fibrosis/cirrhosis, and cancer. While previous work has so far focused mainly on the role of these enzymes in hepatocytes, we will specifically address their role in cholangiocytes and macrophages. We will explore whether dysregulation of lipid hydrolysis activates pro-inflammatory, pro-fibrogenic, and pro-carcinogenic pathways, which might become amenable to future therapeutic interventions.

Experimental approaches:

The PhD student will address these research questions *in vitro* and *in vivo* using human/mouse cell systems and mouse models that either lack or overexpress human wild-type PNPLA3 or the I148M variant, ATGL/PNPLA2 or CGI-58 either systemically or in specific cells (*i.e.* hepatocytes, cholangiocytes or macrophages). These models will be challenged with bile acids and cholestatic liver injuries utilizing our well established cholestasis phenotyping pipeline including functional (bile acid/fatty acid metabolism), histopathological/immuno-histochemical and molecular characterization (qPCR, Western blotting). Key findings in mice and cells will be validated with tissues from patients suffering from different stages and severity of cholestatic/fatty liver disease and liver cancer. The PhD student will receive in depth training in cell and molecular biology, cell culture work and experimental animal (mouse) models. S/he will analyze the gene expression and metabolic profiles of mouse samples from the experiments in cholestatic mice and human tissue obtained from cholestatic and liver cancer patients supported by our imaging and analytical platforms

within the SFB Lipid Hydrolysis. S/he will also perform the *in vitro* experiments in cholangiocytes, macrophages and liver cancer cells. This project will be conducted in close collaboration with the other project within the SFB Lipid Hydrolysis. Findings from this project are expected to result in novel mechanistic insights into the role and regulation of lipid hydrolysis in cholestatic and metabolic liver diseases including new prognostic and therapeutic strategies targeting PNPLA3 and other lipolytic pathways.

References:

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3. Jha P, Knopf A, Koefeler H, Mueller M, Lackner C, Hoefler G, Claudel T, Trauner M. Role of adipose tissue in methionine-choline-deficient model of non-alcoholic steatohepatitis (NASH). *Biochim Biophys Acta*. 2014;1842:959-70
4. Jha P, Claudel T, Baghdasaryan A, Mueller M, Halilbasic E, Das SK, Lass A, Zimmermann R, Zechner R, Hoefler G, Trauner M. Role of adipose triglyceride lipase (PNPLA2) in protection from hepatic inflammation in mouse models of steatohepatitis and endotoxemia. *Hepatology*. 2014;59:858-69
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