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Research interests

Mechanisms of cell injury and inflammation in cholestatic and metabolic liver diseases, chronic inflammatory bile duct disease (cholangiopathies), pharmacological treatment of cholestatic and fatty liver disease as well as cholangiopathies.

The Hans Popper Laboratory of Molecular Hepatology, led by Prof. Trauner, is focused on the molecular mechanisms of inflammation in cholestatic and metabolic liver diseases with the specific role of bile acid (BAs) in the pathogenesis and treatment of these disorders. Previous work of the applicant has focused on the role of BA-activated nuclear receptors and modified BA derivatives in the regulation of hepatobiliary transport, inflammation, fibrosis as well as cellular proliferation and has resulted in several key publications and two international patents. Emerging evidence suggests that the signaling properties of BA (e.g. through activation of dedicated nuclear and plasma membrane receptors) may play a key role in the control of hepatic and intestinal inflammation and innate immunity.. BA-activated receptors could therefore represent a novel therapeutic strategy for cholestatic liver injury in particular chronic inflammatory bile duct diseases as converging site of BA toxicity, signaling and inflammation.

Thesis projects

Project 1: What is the role of the G-protein coupled BA receptor TGR5 in determining the individual cellular inflammatory response in cholestatic injury?

Bile acids (BAs) may play key role as signaling molecules in the regulation of the hepatic inflammatory response to cholestasis via dedicated BA receptors such TGR5. In this project the student will explore the role of TGR5 in mediating BA effects on the inflammatory response to LPS, oxidative stress and proinflammatory cytokines in isolated liver cells

(cholangiocytes, hepatocytes, stellate cells and Kupffer cells) as well as respective cell lines lacking or overexpressing TGR5 (and for comparison the nuclear receptor FXR). The potential role of TGR5 in-vivo will be addressed in mice overexpressing or lacking TGR5 which will be subjected to cholestatic liver injury (common bile duct ligation, mouse models of sclerosing cholangitis and cholestasis of sepsis). Finally, the student will test whether TGR5 agonists are capable of ameliorating the inflammatory response as well as inflammation-driven fibrosis in cholestasis. The results of this project will clarify the role of TGR5 as potential target in the pathogenesis and treatment of cholestatic and chronic inflammatory bile duct diseases.

Project 2: What are the molecular mechanisms of nor-UDCA in counteracting inflammation in cholangiocytes and liver macrophages (inflammatory liver cell cross talk) in cholestasis?

We have shown that nor-Ursodeoxycholic acid (nor-UDCA) but not (its currently clinically used mother compound) ursodeoxycholic acid (UDCA) reverses sclerosing cholangitis in the *Mdr2/Abcb4* knockout mouse model of chronic hepatic inflammation and liver cancer. This project will address the anti-inflammatory mechanisms of nor-UDCA in isolated liver cell types (i.e. hepatocytes, cholangiocytes, Kupffer cells, stellate cells, endothelial cells). To unravel potential anti-inflammatory mechanisms at the molecular level, the student will focus on key pro-inflammatory transcription factors such as NF-kappaB and activating protein 1, as well as Stat 3, 4, and 5 as key transcription factors involved in innate and adaptive immunity in primary hepatic cells/cell lines and mice lacking key transcription factors such as Stats. To explore potential anti-inflammatory effects beyond cholestatic liver injury, the student will test nor-UDCA in more general inflammatory mouse models of endotoxemia, sepsis (fecal peritonitis), viral hepatitis (lymphocytic choriomeningitis virus) and rheumatoid arthritis. The results of this project should advance our understanding of potential direct anti-inflammatory effects of nor-UDCA as novel therapeutic approach to chronic inflammatory bile duct diseases.

Selected Publications

Schaap FG, **Trauner M**, Jansen PL. Bile acid receptors as targets for drug development. **Nat Rev Gastroenterol Hepatol**. 2014 Jan;11(1):55-67

Recknagel P, Gonnert FA, Westermann M, Lambeck S, Lupp A, Rudiger A, Dyson A, Carré JE, Kortgen A, Krafft C, Popp J, Sponholz C, Fuhrmann V, Hilger I, Claus RA, Riedemann NC, Wetzker R, Singer M, **Trauner M** (shared senior authorship), Bauer M. Liver dysfunction and phosphatidylinositol-3-kinase signalling in early sepsis: experimental studies in rodent models of peritonitis. **PLoS Medicine**. 2012;9(11):e1001338

Moustafa T, Fickert P, Magnes C, Guelly C, Thueringer A, Frank S, Kratky D,Sattler W, Reicher H, Sinner F, Gumhold J, Silbert D, Fauler G, Höfler G, Lass A,Zechner R, **Trauner M**. Alterations in lipid metabolism mediate inflammation, fibrosis, and proliferation

in a mouse model of chronic cholestatic liver injury. **Gastroenterology**. 2012; 142(1):140-151

Baghdasaryan A, Claudel T, Gumhold J, Silbert D, Adorini L, Roda A, VecchiottiS, Gonzalez FJ, Schoonjans K, Strazzabosco M, Fickert P, **Trauner M**. Dualfarnesoid X receptor/TGR5 agonist INT-767 reduces liver injury in the Mdr2-/-(Abcb4-/-) mouse cholangiopathy model by promoting biliary HCO^-_3 output. **Hepatology**. 2011 Oct;54(4):1303-12.

Halilbasic E, Fiorotto R, Fickert P, Marschall HU, Moustafa T, Spirli C, Fuchsbichler A, Gumhold J, Silbert D, Zatloukal K, Langner C, Maitra U, Denk H, Hofmann AF, Strazzabosco M, **Trauner M**. Side chain structure determines unique physiologic and therapeutic properties of nor-Ursodeoxycholic Acid in Mdr2-/- Mice. **Hepatology** 2009; 49: 1972-81.

Fickert P, Wagner M, Marschall HU, Fuchsbichler A, Zollner G, Zatloukal K, Lie J, Waalkes MP, Cover C, Denk H, Hofmann AF, Jaeschke H, **Trauner M**.. 24-nor-ursodeoxycholic acid as novel therapeutic approach to sclerosing cholangitis in Mdr2 (Abcb4) knockout mice. **Gastroenterology** 2006; 130: 465-481.