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Targeting bile acid detoxification for liver diseases

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Bile acids (BA) are largely increased in plasma from cholestatic patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and biliary obstruction. BAs are cytotoxic at high concentrations and their accumulation leads to oxidative stress, apoptosis and subsequent damage to the liver parenchyma. A reduction of BA hepatic levels is therefore an important goal for anti-cholestatic strategies, particularly for the treatment of autoimmune hepatobiliary diseases, such as PBC or PSC. Hepatic glucuronidation, catalyzed by the UDP-glucuronosyltransferase (UGT) 1A3, 1A4, 2B4 and 2B7 enzymes, is viewed as a protective mechanism against BA toxicity. Glucuronidation consists in the transfer of the glucuronosyl group from the uridine 5'-diphosphoglucuronic acid (UDPGA) to active toxic hydrophobic molecules. The resulting products are polar, not toxic and easily excreted. An important consequence of BA glucuronidation is the introduction of an additional negative charge to the molecule, which allows their transport by conjugate-transporters present at the basolateral membrane of hepatocytes. These transporters facilitate BA-glucuronides secretion into the blood, followed by enhanced urinary excretion. Based on this re-routing, BA-glucuronidating enzymes have been proposed as novel targets for future anti-cholestatic drugs. Recent molecular pharmacology investigations performed in our lab revealed that activators of various ligand activated transcription factors, namely FXR, PXR, LXR and PPAR, act as BA glucuronidation inducers in human liver cells and animal models. These encouraging results support a therapeutic potential for these pharmacological nuclear receptor ligands, and clinical studies are currently ongoing to evaluate their BA detoxification and anti-cholestatic properties.

Biography

Olivier Barbier has completed his Ph.D. in Physiology-Endocrinology at Laval University, in 2000. After a postdoctoral fellow at the Lille Pasteur Institute (France), he was recruited by the Faculty of Pharmacy, Laval University as an independent researcher in 2004. He is the director of the Laboratory of Molecular Pharmacology at the Centre de recherche du CHU-Québec (Canada). His research program investigates whether pharmacological modulation of endobiotics glucuronidation would be of therapeutic value for the treatment of metabolic and endocrine diseases. Dr. Barbier has published more than 60 papers in reputed journals, and is currently the editor-in-chief of the "Open Gastroenterology Journal".

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