SFB 35 Colloquia in Membrane Transport

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"Role of canalicular phospholipid export pump ABCB4 for pathogenesis and treatment of cholestatic liver diseases"

Bile is primarily formed by canalicular excretion of bile acids and other biliary constituents including cholesterol, phospholipids, and bilirubin conjugates via specific ATP-binding cassette (ABC) transport-ers. The canalicular phospholipid flippase ABCB4 mediates biliary excretion of phosphatidylcholine which forms mixed micelles with bile acids and cholesterol to protect the bile duct epithelium from the detergent properties of bile acids. Mice with targeted disruption of the Abcb4 gene (Abcb4-/- mice) spontaneously develop sclerosing cholangitis with macroscopic and microscopic features of human primary sclerosing cholangitis. Bile duct injury in these mice is linked to defective biliary phospholipid secretion resulting in an increased concentration of free non-micellar bile acids which subsequently cause bile duct epithelial cell (cholan-giocyte) injury with development of sclerosing cholangitis, severe liver fibrosis and liver tumors (hepa-tocellular carcinomas). In analogy to the Abcb4-/- mouse model of sclerosing cholangitis, hereditary and acquired ABCB4 defects may play a role in the pathogenesis of a broad spectrum of hepatobiliary diseases in humans ranging from progressive familial intrahepatic cholestasis in neonates to intra-hepatic cholestasis of pregnancy, drug-induced cholestasis, intrahepatic cholelithiasis, non-anastomotic biliary strictures after liver transplantation, sclerosing cholangitis and biliary cirrhosis in adults. Therapeutic strategies for these disorders may target bile composition/toxicity via key nuclear receptors therapeutically used bile acid ursodeoxycholic acid (UDCA) shows some of these properties, but has limited efficacy in the treatment of sclerosing cholangitis and other cholestatic disorders in humans. In contrast to UDCA, its side chain-shortened homologue norUDCA undergoes cholehepatic shunting between cholangiocytes and hepatocytes leading to a bicarbonate-rich hypercholeresis counteracting bile acid toxicity. Moreover, norUDCA has direct has anti-inflammatory, anti-fibrotic and anti-proliferative effects in hepatocytes, cholangiocytes and myofibroblasts. norUDCA is able to reverse the disease phenotype in the Abcb4-/- mouse model of sclerosing cholangitis. Upcoming clinical trials will have to demonstrate whether norUDCA or other side chain-modified bile acids are also clinically effec-tive in humans.