Abstract

Identification and functional characterization of numerous transport systems at the sinusoidal and canalicular membrane of hepatocytes have significantly expanded our understanding of bilirubin metabolism and contributed to elucidation of molecular basis of hereditary jaundice. Moreover, dysregulation of hepatobiliary transport systems could explain jaundice in many acquired liver disorders. This thesis is focused on the new aspects of bilirubin handling in hepatocytes based on elucidation of the molecular basis of Rotor syndrome.

The first study is focused on the antioxidative properties of bilirubin in liver tissue in a model of obstructive cholestasis. In the second part of the thesis we present several novel mutations in *ABCC2*, the gene associated with Dubin-Johnson syndrome, identified in patients selected for the Rotor locus mapping study. In the key third study concerned with Rotor syndrome we demonstrated that biallelic inactivating mutations causing complete absence of transport proteins OATP1B1 and OATP1B3 result in disruption of hepatic reuptake of bilirubin, which is the molecular basis of Rotor-type jaundice. These results indicate that apart from secretion of conjugated bilirubin into bile, a significant fraction of bilirubin glucuronide is secreted via MRP3 into sinusoidal blood and subsequently reuptaken by sinusoidal transporters OATP1B1 and OATP1B3. We further confirmed that Rotor proteins are down-regulated in advanced stages of cholestatic liver disorders. We demonstrated that OATP1Bs expression inversely correlates with serum levels of conjugated and total bilirubin. We suppose that aside from increased MRP3 expression, down-regulation of OATP1B1 and OATP1B3 contributes to conjugated hyperbilirubinemia in advanced liver diseases with predominantly obstructive type of cholestasis.

Keywords: Bilirubin, hyperbilirubinemia, jaundice, cholestasis