Hepatic Transporters in Cholestatic Liver Diseases and Molecular Targetting Medical Treatments

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Cholestatic liver diseases are often found in daily clinical practice. Decreased canalicular secretion of bile acid and a broad range of anionic conjugates such as bilirubin diglucuronide is a fundamental pathophysiological defect in all forms of cholestasis. Oxidative stress associated with cholestasis underlies the development of jaundice and hepatic fibrosis.

Experimental cholestasis has been associated with impaired Mrp2- and Bsep-mediated hepatobiliary transport as well as down-regulation and altered localization of Mrp2 and Bsep. This provides the molecular basis for the development of cholestasis. Based on the results of clinical study, the diminished canalicular membrane localization of Mrp2 and Bsep was closely associated with the impairment of bile formation and secretion in the patients with cholestatic liver diseases.

Under cholestatic conditions (associated with jaundice), the Keap1-Nrf2 system, which functions as a stress sensor, is activated in the livers and causes intrinsic hepatocellular adaptive induction of transporters and antioxidative stress gene products to prevent ongoing liver injury. However, intrinsic adaptation in cholestasis is reportedly weak. Our recent studies have shown that the expression of Mrp family members, detoxifying enzymes and antioxidative stress gene products via the Nrf2-transcriptional pathway are markedly up-regulated in the livers of animals treated with bile acid or ingredients of an herbal medicine.

Therefore, stimulation and restoration of expression and function of Mrp family members and induction of potent detoxification and antioxidative stress systems by Nrf2 activation may be an important target for specific pharmacotherapeutic interventions in the treatment of cholestatic liver diseases.