CCI-14

Roles of the prostaglandin I_2-IP system in the development of nonalcoholic steatohepatitis

Shima Kumei[1,2,4], Koh-ichi Yuhki[1,4], Fumiaki Kojima[1,4], Hitoshi Kashiwagi[1,4], Toshikatsu Okumura[2], Shuh Narumiya[3,4], Fumitaka Ushikubi[1,4]

[1]Department of Pharmacology, Asahikawa Medical University, Asahikawa
[2]Department of General Medicine, Asahikawa Medical University, Asahikawa
[3]Department of Pharmacology, Kyoto University Graduate School of Medicine, Kyoto
[4]CREST, Japan Science and Technology Agency, Tokyo

Abstract

Nonalcoholic steatohepatitis (NASH) is a hepatic manifestation of metabolic syndrome and presents a global health issue. NASH is characterized by hepatic steatosis, inflammation and fibrosis, with increased risks for cirrhosis and hepatocellular carcinoma. Prostaglandin (PG) I_2 receptor IP is expressed broadly in the liver. In addition, cyclooxygenase (COX)-2, a rate-limiting enzyme for prostanoid biosynthesis, is up-regulated in the liver of NASH patients. However, roles of PGI_2 in the development of NASH remain to be determined. Here, we investigated the role of the PGI_2-IP system in the development of NASH using mice lacking IP ($IP^{-/-}$ mice). Wild-type (WT) mice fed with methionine- and choline-deficient (MCD) diet developed NASH. Interestingly, $IP^{-/-}$ mice had earlier development of NASH with augmented steatosis and prominent inflammatory cell infiltration. Furthermore, $IP^{-/-}$ mice had higher hepatic iron deposition than WT mice, resulting in prominent oxidative stress. Accordingly, an IP agonist beraprost improved biochemical and histological parameters of NASH in WT mice. These results indicate that PGI_2 plays a crucial role in the development of NASH, and stimulation of IP signaling might be an attractive therapeutic strategy for NASH.