The prostaglandin E_2-EP4 system protects the liver in Concanavalin A-induced hepatitis

Yoshitaka Imamichi[1], Koh-Ichi Yuhki[1], Hitoshi Kashiwagi[1], Shima Kumei[1], Katsura Nakanishi[1], Fumiaki Kojima[2], Shuh Narumiya[3], Fumitaka Ushikubi[1]

[1]Dept. Pharmacol., Asahikawa Med. Univ., [2]Dept. Pharmacol., Kitasato Univ., [3]Dept. Drug Discovery Medicine, Kyoto Univ. Grad. Sch. Med.

Concanavalin A (Con A) induces hepatitis in mice, an established model of acute immune-mediated hepatitis. Con A up-regulated the hepatic expression of prostaglandin E_2 (PGE_2) synthetic enzymes and PGE_2 receptor subtype EP4. Therefore, we examined the role of the PGE_2-EP4 system in Con A-induced hepatitis. Con A-induced increases in serum transaminase (AST and ALT) levels were significantly higher in EP4-deficient mice than those in wild-type mice. Accordingly, the size of necrotic areas in the liver was significantly greater in EP4-deficient mice than that in wild-type mice, indicating the protective role of the PGE_2-EP4 system. Increases in the expression levels of mRNAs for interleukin-22 (IL-22), a liver protective cytokine, and IL-22 receptor (IL-22Ra1) were significantly lower during the early phase of hepatitis in EP4-deficient mice than those in wild-type mice after Con A administration. In addition, increase in the expression level of mRNA for Interleukin-23 subunit alpha (IL-23a) which is important for IL-22-producing cell differentiation, was also significantly lower in EP4-deficient mice. In primary-cultured hepatic nonparenchymal cells (NPCs), which include macrophages and T cells, PGE_2 and IL-23 synergistically up-regulated the IL-22 gene expression, and the increase was significantly lower in NPCs from EP4 deficient mice than that from the wild-type mice. These results indicate that PGE_2-EP4 system protects the liver at least through the activation of the IL-23/IL22 axis of NPCs in Con A-induced hepatitis.