論 文 要 旨

Human neutrophil peptide-1 promotes alcohol-induced hepatic fibrosis and hepatocyte apoptosis

指宿 りえ

BACKGROUND AND AIMS: Neutrophil infiltration of the liver is a typical feature of alcoholic liver injury. Human neutrophil peptide (HNP)-1 is an antimicrobial peptide secreted by neutrophils. The aim of this study was to determine if HNP-1 affects ethanol-induced liver injury and to examine the mechanism of liver injury induced by HNP-1.

METHODS: Transgenic (TG) mice expressing HNP-1 under the control of a β-actin-based promoter were established. Ethanol was orally administered to HNP-1 TG or wild-type C57BL/6N (WT) mice. SK-Hep1 hepatocellular carcinoma cells were used to investigate the effect of HNP-1 on hepatocytes *in vitro.*

RESULTS: After 24 weeks of ethanol intake, hepatic fibrosis and hepatocyte apoptosis were significantly more severe in TG mice than in WT mice. Levels of CD14, TLR4, and IL-6 in liver tissues were higher in TG mice than in WT mice. Apoptosis was accompanied by higher protein levels of caspase-3, caspase-8, and cleaved PARP in liver tissue. In addition, phosphorylated ASK1, ASK1, phosphorylated JNK, JNK1, JNK2, Bax, Bak and Bim were all more abundant in TG mice than in WT mice. In contrast, the level of anti-apoptotic Bcl2 in the liver was significantly lower in TG mice than in WT mice. Analysis of microRNAs in liver tissue showed that miR-34a-5p expression was significantly higher in TG mice than in WT mice. Furthermore, in the presence of ethanol, HNP-1 increased the apoptosis with the decreased level of Bcl2 in a concentration-dependent manner *in vitro*.

CONCLUSIONS: HNP-1 secreted by neutrophils may exacerbate alcohol-induced hepatic fibrosis and hepatocyte apoptosis with a decrease in Bcl2 expression and an increase in miR-34a-5p expression.