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氏名	加藤　寛之
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論文審査担当者	主査：　城 卓志 副査：　竹山 廣光，高橋 智

Abstract

There is abundant epidemiological evidence that heavy alcohol intake contributes to hepatocellular carcinoma (HCC) development (Torre LA et al, 2015). Previous reports indicated that connexin 32 (Cx32), which is a major hepatocyte gap junction protein, is downregulated in chronic liver disease and has a protective role in hepatocarcinogenesis (Nakashima Y et al, 2004; Yamaoka K et al, 2000). However, functions of Cx32 in alcohol-related hepatocarcinogenesis have not been clarified. To evaluate them, 9-week-old Cx32 dominant negative transgenic (Tg) rats and their wild-type (Wt) littermates were given 1 % or 5 % ethanol (EtOH) or water ad libitum, for 16 weeks after an intraperitoneal injection of diethylnitrosamine (200 mg/kg). EtOH significantly increased the incidence and multiplicity of HCC and total tumors in a dose-dependent manner in Tg rats, but not in Wt rats. Although the number and area of glutathione S-transferase placental form (GST-P) positive foci were not significantly different between the groups, EtOH increased the Ki-67 labeling indices in GST-P positive foci only in Tg rats. EtOH up-regulated phosphorylated Erk1/2 with decrease of the Erk1/2 inhibitor, dual specificity protein phosphatase 1 (Dusp1) in whole livers of Tg and Wt rats. Immunofluorescence staining and quantitative RT-PCR revealed that EtOH significantly increased nucleolar localization of phosphorylated Erk1/2 and contrastingly reduced Dusp1 protein and mRNA expression in GST-P positive foci and HCC of Tg rats as compared to those of Wt rats. These findings suggest that Cx32 dysfunction like in chronic liver disease promoted EtOH-associated hepatocarcinogenesis through dysregulation of Erk-Dusp1 signaling.