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Connexin 32 and luteolin play protective roles in nonalcoholic steatohepatitis development and its related hepatocarcinogenesis in rats

Abstract

Non-alcoholic fatty liver disease comprises a spectrum of diseases ranging from simple steatosis to steatohepatitis [non-alcoholic steatohepatitis (NASH)], fibrosis and ultimately cirrhosis. NASH has the potential to lead to the development of hepatocellular carcinoma (HCC). Connexin (Cx) 32, a major gap-junctional (GJ) protein of hepatocytes, plays an important role in liver tissue homeostasis. Cx 32 plays a preventive role in hepatocarcinogenesis. However, the precise contribution of Cx32 in the development of NASH has not been established. In this study, we aimed to clarify the role of Cx32 and the chemopreventive effect of luteolin, an antioxidant flavonoid, on the progression of NASH and NASH-related hepatocarcinogenesis. Cx32 dominant negative transgenic (Cx32ΔTg) and wild-type (Wt) rats at 10 weeks of age were given diethylnitrosamine and fed methionine–choline-deficient diet (MCDD) or MCDD with luteolin for 12 weeks. MCDD induced steatohepatitis and fibrosis along with increased inflammatory cytokine expression and reactive oxygen species in the liver. These effects were more severe in Cx32ΔTg rats as compared with Wt rats, and significantly suppressed by luteolin in both genotypes. Concerning NASH-related hepatocarcinogenesis, the number of glutathione S-transferase placental form (GST-P)-positive foci was greater in Cx32ΔTg versus Wt rats, and significantly reduced by luteolin in Cx32ΔTg rats. Microarray analysis identified brain expressed, X-linked 1 (Bex1) as an upregulated gene in Cx32ΔTg rat liver. Quantitative RT-PCR and *in situ* hybridization revealed that increased Bex1 mRNA was localized in GST-P-positive foci in Cx32ΔTg rats, and the expression level was significantly decreased by luteolin. Moreover, Bex1 knockdown resulted in significant growth inhibition of the rat HCC cell lines. These results show that Cx32 and luteolin have suppressive roles in inflammation, fibrosis and hepatocarcinogenesis during NASH progression, suggesting a potential therapeutic application for NASH.