The roles of gap junctional intercellular communication in non-alcoholic steatohepatitis (NASH) and liver fibrosis

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Non-alcoholic steatohepatitis (NASH) is a common risk factor for fibrosis, cirrhosis, and a predisposing factor for the development of hepatocellular carcinoma. Increase of incidence of NASH has become as a major worldwide public health problem. Connexin (Cx)32, a hepatocyte gap-junction protein, plays an important role in liver tissue homeostasis. However, the precise contribution of Cx32 in the development of NASH and fibrosis has not been established. Therefore, roles of Cx32 on NASH and fibrosis was explored by using Cx32 dominant negative transgenic (Cx32ΔTg) rat model. Extensive fibrosis was evident in Cx32ΔTg as compared to wild-type (Wt) rats; the developing fibrous septa were extended not only from the portal area to the centrilobular zone but also to adjacent portal tracts. Cirrhosis with bridging fibrosis was also recognized in some Cx32ΔTg rat livers. Elevasion of reactive oxygen species, inflammatory cytokine expressions (Tnfα, Il6, Tgfβ, Il1β, Timp2 and Col1a1), and NF-κB activity were clearly severe in Cx32ΔTg rats and these changes and fibrosis was suppressed by some anti-oxidants. These results suggest that accumulation of oxidative stress induced by Cx32 dysfunction contributes to fibrogenic remodeling in the liver. We would like to discuss about molecular mechanisms and chemoprevention of NASH and liver fibrosis.