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Involvement of senescence marker protein-30 (SMP30) on the Smad3-dependent hepatic injury

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Smad3 is a key modulator of the transforming growth factor-β1 (TGF-β1) signaling pathway. TGF-β1 is thought to be an important cytokine in the regulation of the accumulation of extracellular matrix protein during the hepatic injury. Firstly, to investigate the influence of Smad3 on liver fibrogenesis, we observed histopathological findings and the remarkable protein expression of Smad3-null mice liver after four weeks of CCl_4 treatment. In Smad3-null mice, CCl_4-induced liver fibrosis was mild grade compared with the $Smad3^{+/+}$ mice. In a comparative proteomic analysis, differently expressed proteins of the CCl_4-treated Smad3-null mice were identified as antioxidant-related proteins, such as the senescence marker protein-30 (SMP30), selenium-binding proteins (SP56) and glutathione S-transferases (GSTs). These results indicate that the Smad3 pathway was in correlation with the antioxidant defense system within liver injuries. In conclusion, these data suggest that the alteration of SMP30, by the lack of Smad3 activation, had an influence on the inhibition of TGF-β1-mediated liver damage. Furthermore, the specific control of Smad3-relavent proteins (SMP30) may play a critical role in the prevention of liver diseases. Therefore, we evaluated the CCl4-induced acute hepatotoxicity in SMP30-deficient mice to investigate the precise roles of SMP30 in the liver. SMP30 was discovered as aging marker molecule on the aging status with androgen-independent. Others report indicated that SMP30 deficiency causes activation of lipids accumulation in the liver and controlling the antioxidant enzyme activity. In the present study, at 24 hr after the CCl_4 injection, blood and liver tissues of all mice were collected for serum and histopathological analysis. In the CCl_4-treated groups, elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the degrees of centrilobular necrosis and inflammation were significantly observed ($P < 0.01$). However, in the Vitamin C-treated groups, the degrees of liver damages were slightly inhibited. The inhibition of liver damage due to the Vitamin C treatment was more distinguished in the $SMP30^{-/-}$ (KO) mice compared to those in the $SMP30^{+/+}$ (WT) mice. These date indicate that administration of Vitamin C may be a pivotal factor in $SMP30^{-/-}$ (KO) mice and enhancer of hepatoprotective effect of SMP30. The expressions of Smad3 and p-Smad3 were more changed in the $SMP30^{-/-}$ (KO) mice compared to those in the $SMP30^{+/+}$ (WT) mice after CCl_4 injury. In particular, expression of p-Smad3 in the $SMP30^{-/-}$ (KO) mice was significantly matched in our previous experiments for hepatic fibrogenesis of Smad3 null mice. These results indicate that the deficiency of SMP30 have an influence on the induction of Smad3 within liver injuries. In conclusion, these data suggest that the SMP30 may be critical control factor for hepatic injury, mediated by inhibition of TGF-β1 signaling and $SMP30^{-/-}$ (KO) mice could be useful animal model for oxidative status-related liver injury. From this study, we recognized the SMP30 protein play a protective role in hepatic injury and the expression of SMP30 present the alteration of Smad3 pathway. Moreover in the proteomic analysis, we performed that the SMP30-related proteins were identified in the $SMP30^{+/+}$ (WT) and $SMP30^{-/-}$ (KO) mice liver tissue. We'd like to suggest that several SMP30-related proteins were significantly changed in protective process of acute hepatic injury.

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