Identification of Hic-5 as a novel fibrogenic gene for liver fibrosis through downregulation of Smad7.

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Background & Aim: Hydrogen peroxide-inducible clone-5 (Hic-5), also named as transforming growth factor beta-1-induced transcript 1 protein (Tgfb1i1), was found to be induced by TGF-β. Previous studies have shown that TGF-β is a principal mediator of hepatic stellate cell (HSC) activation in liver fibrosis. However, this process remains elusive. In this study, we aimed to define the role of Hic-5 in HSC activation and liver fibrosis.

Methods: we examined the expression levels of Hic-5 during HSCs activation and in fibrotic liver tissues by quantitative real-time reverse transcriptase polymerase chain reaction, western blot and immunohistochemistry. Hic-5 knockout (KO) and wild type (WT) mice were subjected to bile duct ligation (BDL) or carbon tetrachloride (CCl₄) injection to induce liver fibrosis.

Results: Hic-5 expression was strongly upregulated in TGF-β activated HSCs of the human fibrotic liver tissue and BDL or CCl₄ induced mouse liver fibrosis. Hic-5 deficiency significantly attenuated mouse liver fibrosis and HSC activation. Furthermore, Hic-5 knockdown by siRNA in vivo repressed CCl₄-induced liver fibrosis in mice. Mechanistically, the absence of Hic-5 significantly inhibited the TGF-β/Smad2 signaling pathway, proved by increasing Smad7 expression, resulting in reduced collagen production and α-smooth muscle actin expression in the activated HSC.

Conclusion: Hic-5 deficiency attenuates the activation of HSCs and liver fibrosis though reducing the TGF-β/Smad2 signaling by upregulation of Smad7. Thus, Hic-5 can be regarded as a potential therapeutic target for liver fibrosis.

Key words: Hic-5, Smad7, hepatic stellate cells, liver fibrosis