A key role of CUG-binding protein 1 in HSC activation and liver fibrogenesis revealed by fraxinellone

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Excessive activation of hepatic stellate cells (HSCs) is a key step in liver fibrogenesis. Here we report that CUG-binding protein 1 (CUGBP1) expression is elevated in HSCs and positively correlates with liver fibrosis severity in human liver biopsies. Transforming growth factor beta (TGF- β) selectively increases CUGBP1 expression in cultured HSCs in a p38 mitogen-activated protein kinase (MAPK)-dependent manner. Knockdown of CUGBP1 inhibits alpha smooth muscle actin (α -SMA) expression and promotes interferon gamma (IFN- γ) production in HSCs in vitro. We further show that CUGBP1 specifically binds to the 3' untranslated region (UTR) of human IFN- γ mRNA and promotes its decay. In mice, knockdown of CUGBP1 alleviates, whereas its overexpression exacerbates, bile duct ligation (BDL)-induced hepatic fibrosis. Therefore, CUGBP1-mediated IFN- γ mRNA decay is a key event for profibrotic TGF- β -dependent activation of HSCs, and inhibiting CUGBP1 to promote IFN- γ signaling in activated HSCs could be a novel strategy to treat liver fibrosis.