Hepatitis C Virus Core Protein Stimulates Fibrogenesis via Obese Receptor in Hepatic Stellate Cells

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Hepatitis C Virus (HCV) core protein (HCVcp), which is secreted by infected cells, is reported as an immunomodulator in immune cells. However, the effects of HCVcp on hepatic stellate cells (HSCs), the key cells in liver fibrosis, still remain unclear. In this study, we investigated the effects of HCVcp on obese receptor (ObR) related downstream signaling pathways and fibrogenic gene expressions in HSCs. LX-2, a human hepatic stellate cell line, was incubated with HCVcp. Inhibitors and short interfering RNAs were used to interrogate the mechanisms of HCVcp on HSCs. HCVcp-stimulated protein expressions of α-smooth muscle actin (α-SMA) and gp91phox were reversed by NADPH oxidase inhibitor, but not JAK inhibitor. Short interfering RNA for Ob-Rb downregulated HCVcp-induced STAT3, AKT and AMPKα phosphorylation, and reversed HCVcp-reduced mRNA expressions of matrix metalloproteinase (MMP)-1, peroxisome proliferator-activated receptor (PPAR)γ and sterol regulatory element binding protein-1c (SREBP-1c). Knockdown of STAT3 gene reversed HCVcp-stimulated MMP-1 mRNA downregulation. HCVcp stimulated reactive oxygen species (ROS) formation, which in turn induced phosphorylation of AKT, leading to repression of PPARγ and SREBP-1c genes. Blocking of AMPKα signaling reversed HCVcp-caused SREBP-1c mRNA suppression. Our results suggest that HCVcp-induced HSC activation is associated with Ob-Rb -mediated JAK2-STAT3, AMPK and AKT signaling pathways. The study bears implications for treating liver fibrosis due to HCV infection.