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Estrogen Controls Hepatitis C Virus Entry and Spread through the GPR30 Pathway

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Abstract : Hepatitis C virus (HCV)-associated hepatocellular carcinoma, fibrosis and cirrhosis are more frequent in men and postmenopausal women than in premenopausal women and women receiving hormone replacement therapy, suggesting that β-estradiol (estrogen) plays an innate role in preventing viral infection and liver disease. Estrogen classically acts through nuclear estrogen receptors or, alternatively, through the membrane-bound G-protein-coupled estrogen receptor (GPR30 or GPER). We observed a marked decrease in detectable virus when HCV-infected human hepatoma cells were treated with estrogen. The effect was mimicked by both Tamoxifen (Tam) and G1, a GPR30-specific agonist, and was reversed by the GPR30-specific antagonist, G15. Through GPR30, estrogen-mediated the down-regulation of occludin; a tight junction protein and HCV receptor, by promoting activation of matrix metalloproteinases (MMPs). Activated MMP-9 was secreted in response to estrogen, cleaving occludin in the extracellular Domain D, the motif required for HCV entry and spread. This pathway gives new insight into a novel innate immune pathway and the disparate host-virus responses to HCV demonstrated by the two sexes. Moreover, these data suggest that hormone replacement therapy may have beneficial antiviral properties for HCV-infected postmenopausal women and show promise for new antiviral treatments for both men and women.

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