Matrix Conditions and KLF2-Dependent Induction of Heme Oxygenase-1 Modulate Inhibition of HCV Replication by Fluvastatin.

Abstract:
HMG-CoA-reductase-inhibitors (statins) have been shown to interfere with HCV replication in vitro. We investigated the mechanism, requirements and contribution of heme oxygenase-1 (HO-1)-induction by statins to interference with HCV replication. HO-1-induction by fluvasta-, simva-, rosuva-, atorva- or pravastatin was correlated to HCV replication, using non-infectious replicon systems as well as the infectious cell culture system. The mechanism of HO-1-induction by statins as well as its relevance for interference with HCV replication was investigated using transient or permanent knockdown cell lines. Polyacrylamide (PAA) gels of different density degrees or the Rho-kinase-inhibitor Hydroxyfasudil were used in order to mimic matrix conditions corresponding to normal versus fibrotic liver tissue. All statins used, except pravastatin, decreased HCV replication and induced HO-1 expression, as well as interferon response in vitro. HO-1-induction was mediated by reduction of Bach1 expression and induction of the Nuclearfactor (erythroid-derived 2)-like 2 (NRF2) cofactor Krueppel-like factor 2 (KLF2). Knockdown of KLF2 or
HO-1 abrogated effects of statins on HCV replication. HO-1-induction and anti-viral effects of statins were more pronounced under cell culture conditions mimicking advanced stages of liver disease. Statin-mediated effects on HCV replication seem to require HO-1-induction, which is more pronounced in a microenvironment resembling fibrotic liver tissue. This implicates that certain statins might be especially useful to support HCV therapy of patients at advanced stages of liver disease.