Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis c virus core protein

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摘要.

Abstract

We have demonstrated previously that the core protein of hepatitis C virus (HCV) exhibits suppression activity on gene expression and replication of hepatitis B virus (HBV). Here we further elucidated the suppression mechanism of HCV core protein. We demonstrated that HCV core protein retained the inhibitory effect on HBV gene expression and replication when expressed as part of the full length of HCV polyprotein. Based on the substitution mutational analysis, our results suggested that mutation introduced into the bipartite nuclear localization signal of the HCV core protein resulted in the cytoplasmic localization of core protein but did not affect its suppression ability on HBV gene expression. Mutational studies also indicated that almost all dibasic residue mutations within the N-terminal 101-amino acid segment of the HCV core protein (except Arg39 – Arg40) impaired the suppression activity on HBV replication but not HBV gene expression. The integrity of Arg residues at positions 101, 113, 114, and 115 was found to be essential for both suppressive effects, whereas the Arg residue at position 104 was important only in the suppression of HBV gene expression. Moreover, our results indicated that the suppression on HBV gene expression was mediated through the direct interaction of HCV core protein with the trans-activator HBx protein, whereas the suppression of HBV replication involved the complex formation between HBV polymerase (pol) and the HCV core protein, resulting in the structural incompetence for the HBV pol to bind the package signal and consequently abolished the formation of the HBV virion. Altogether, this study suggests that these two suppression effects on HBV elicited by the HCV core protein likely depend on different structural context but not on nuclear localization of the core protein, and the two effects can be decoupled as revealed by its differential targets (HBx or HBV pol) on these two processes of the HBV life cycle.