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The Repressive Activity of Hepatitis C Virus Core Protein on the Transcription of p21 is Regulated by PKA-Mediated Phosphorylation

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HCV core protein is known to repress the transcription of p21 directly in a p53-independent manner. In this study, the region of HCV core protein responsible for the transcriptional repression of p21 promoter was determined. N-terminal half of core protein almost completely lost the ability to repress p21 promoter, indicating that the domain required for the majority of p21 repression is located between amino acid positions 91 and 191. The *trans*-repression activity of HCV core mutant S99L on p21 gene expression was similar to that of wild type core protein whereas mutation of the 116th amino aicd Ser into either Ile or Ala complely abolished the repressive ability of HCV core protein. In addition, the trans-repression activity of HCV core mutant S116N was similar to that of wild type core protein, suggesting that an acidic aspartate residue can mimic the effect of phosphorylation. When treated with a PKA inhibitor (HA1004), the inhibitory activity of wild-type HCV core protein was dose-dependently decreased and was completely lost at the concentration of 5 μM. On the contrary, the repression activity of HCV core protein was increased by treatment with a PKA activator, indicating that the p21 repressive activity of HCV core protein is regulated by phosphorylation at S-116 by PKA. The growth rate of HCV Core-expressing cell line was about 2 fold higher compared to that of the parent cells, suggesting that the repression of p21 transcription by HCV core protein is actually connected to the stimulation of cell growth.