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The repressive activity of hepatitis C virus core protein on the transcription of p21^{waf1} is regulated by protein kinase A- mediated phosphorylation

Eun Young Jung[a], Mi Nam Lee[a], Hyo Young Yang[a], Dae-Yeul Yu[b], Kyung Lib Jang[a,*]

[a]Department of Microbiology, College of Natural Sciences, Pusan National University, Pusan 609-735, Republic of Korea.

Hepatitis C virus (HCV) core protein is known to repress the transcription of p21waf1 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 84 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 acid Ser into either Ile or Ala completely abolished the repressive ability of HCV core protein. In addition, the *trans*-repression activity of HCV core mutant S116D 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 protein kinase A inhibitor, H-89, 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, dibutyryl-cAMP, indicating that the p21 repressive activity of HCV core protein is regulated by phosphorylation at S-116 by protein PKA