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Transcriptional repression of $p21^{waf1}$ by hepatitis C virus NS3 protein in a p53-dependent pathway

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Hepatitis C virus NS3 protein is known to affect normal cellular functions, such as cell proliferation and cell death, and being involved, either directly or indirectly, in HCV hepatocarcinogenesis. In this study, we demonstrated that NS3 protein could specifically repress the promoter activity of p21 in a dose-dependent manner. The effect was not cell type specific and was synergistic when combined with HCV core protein. The repression of the p21 promoter by NS3 was almost completely lost when p53 binding sites present on the p21 promoter were removed. Furthermore, p53 binding sites were sufficient to confer a strong NS3 responsiveness to an heterologous promoter, suggesting that NS3 represses the transcription of p21 by modulating the activity of p53. Although the NS3 protein domain required for the majority of p21 repression was located on the protease domain, the proteinase activity itself does not seem to be necessary for the repression of p21 promoter. Both transcription and protein stability of p53 was not affected by NS3, suggesting that NS3 might repress transcription of p21 by inhibiting the regulatory activity of p53 via protein-protein interaction(s). Finally, the growth rate of NS3-expressing cell lines was at least two times faster compared to that of the parent NIH 3T3 cells, indicating that the repression of p21 is actually reflected by the stimulation of cell growth.