Genotype-specific Effects of HCV Frame-shift (F) Protein in Interferon Induction and Response Pathways

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Background/Objective

Type I interferons (IFN) are the first line of defense against virus infection. Production of IFN might induce hundreds of IFN stimulated genes (ISGs) to establish an antiviral state in the infected cells. Hepatitis C Virus (HCV) has evolved mechanisms to evade innate immunity, resulting in chronic infections. It has been reported that HCV Core protein can interfere with the IFN signaling pathway, but these studies did not exclude the contributions of F protein, which is a frameshift product of Core coding sequence. F protein is produced during natural HCV infection, and the titers of anti-F antibody are significantly higher in the group of chronically infected patients. Our research is to investigate that whether the F protein plays a role in IFN induction and signaling pathway.

Method

We engineered F expression constructs from Core coding sequences of 4 genotypes (1a, 2a, 3a and 4a) of HCV as well as the sequences which would only be able to produce Core protein. To investigate the function of F protein in type I IFN induction and response pathway, we performed luciferase reporter assay of IFN β and ISRE promoters. Different ISG mRNA expressing levels were also confirmed by real-time PCR.

Result

The peptide lengths and amino acids sequences of Core proteins were conserved, but those of F proteins were highly variable. Therefore, we hypothesized that the F protein from different genotypes might control the type I IFN production and response differently to evade innate immunity. Both IFN β and ISRE promoter activities were enhanced in genotype 1a F protein expressing cells, but reduced in genotype 2a F protein expressing cells.

Conclusion

F proteins of HCV are involved in both IFN β induction and response signaling pathways. Further molecular mechanism how F proteins from different genotypes of HCV control these pathways differently will be investigated and discussed.