Hepatitis C virus promotes the expression of oncogenic isoform of ErB3 binding protein 1 (Ebp1) by modulating the alternate splicing of Ebp1 mRNA

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Persistent hepatitis C virus (HCV) infection leads to chronic hepatitis C (CHC), which often progresses to liver cirrhosis (LC) and hepatocellular carcinoma (HCC). HCV modulates the function of multiple host factors to establish its persistent infection and triggers post-infection pathogenesis. We have recently identified a cell factor, ErbB3 binding protein 1 (Ebp1), which specifically interacts with the viral nonstructural proteins and strongly inhibits HCV replication. Ebp1 has two different isoforms, p48 and p42, resulting from differential splicing. The longer isoform, p48, is anti-apoptotic and oncogenic which promotes HCV replication while shorter isoform, p42, is pro-apoptotic and tumor suppressor which strongly inhibits viral replication. We found that in HCV infected cells, the oncogenic form of Ebp1-p48 is abundantly expressed as compared to mock infected control cells. Analysis of mRNA levels of each of the isoforms revealed that greater than 95% of total Ebp1 mRNA corresponds to the oncogenic p48 isoform in HCV infected cells. In contrast, opposite results were obtained in control cell where majority of Ebp1 mRNA corresponded to tumor suppressor p42 isoform. These results indicate the mechanism by which HCV may have inhibitory effect on the expression of p42 isoform by blocking alternate splicing events of Ebp1 pre-mRNA and promoting selective expression of oncogenic p48 isoform. MH14 cells were used for all experiments. MH14 cells are a derivative of the Huh7 cell line, which carries stable HCV subgenomic replicons. To determine the mRNA level of p42 and p48 isoforms in HCV infected and uninfected control cells, we used specific primers for RT-PCR of Ebp1-p48 isoform as we well as total Ebp1. The level of Ebp1-p42 isoform was determined by subtracting the level of p48 mRNA from total Ebp1 mRNA level.

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Biography

Vaishali Pandey is a high school summer intern in the Department of Microbiology at the New Jersey Medical School, Rutgers University. She has been mentored and trained in Molecular Biology and Virology by Dr. Alok Upadhyay. She has contributed significantly on this project and has determining the transcript levels of Ebp1 isoforms in HCV infected and uninfected cells.