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 (Ebp-1), 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.