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Modeling HCV Interactions with p53: Implications for Carcinogenesis

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Infection with Hepatitis C virus (HCV) has reached epidemic proportions; it is one of the least tested for, but often one of the most dangerous silent killers among Americans. Individuals with chronic HCV infection and without access to treatment are at high risk for developing Hepatocellular Carcinoma (HCC), a liver cancer that is rapidly fatal after diagnosis. A number of factors have been identified that can contribute to HCV-driven carcinogenesis such as scarring of the liver, and chronic inflammation. However, it remains unknown whether cancer arises in infected or uninfected hepatocytes. Recently, strong evidence has emerged that shows HCV can directly interact with the tumor suppressor protein p53, thereby modulating its action. Normally, if a cell has DNA damage, p53 will be activated and the cell shall either be prompted to either repair this damage, or undergo apoptosis if the damage is too great. In the presence of low levels of HCV, p53 activity is enhanced which might afford a higher degree of protection against the malignant transformation of infected hepatocytes. This effect is reversed when HCV levels are high – p53 activity is then suppressed which might exaggerate the chances of cancer arising in an infected cell. Unfortunately, the mechanism underlying this non-linear and non-monotonic effect of HCV on p53 remain to be elucidated. Here, we present a biochemically-motivated mathematical model of HCV-p53 interactions and show that a direct interaction between HCV and p53 is insufficient to recapitulate the experimental data. We hypothesize the existence of an additional factor that is activated under high levels of HCV and that inhibits p53 function, and present experimental evidence for such a factor to exist. Finally, using a previously published model of the oscillatory response of p53 to DNA damage, we simulate the effect of varying the degree of HCV expression on the ability of the infected hepatocyte to repair DNA damage. These findings can have a crucial impact not only on further explicating the pathway to carcinogenesis in HCV patients, but may also present a potential therapeutic target that could help in preventing at least some these cases.