



SYSTEMS BIOLOGY OF HEPATITIS C VIRUS REPLICATION

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Hepatitis C virus (HCV) infection is a major global health problem, with 170 million chronically infected individuals worldwide. A main obstacle in treatment is the insidious course of the disease; HCV infection persists in about 80% of patients and is mostly asymptomatic. However, these persons are at high risk to develop liver cirrhosis and hepatocellular carcinoma. There is no vaccine available against HCV, and current treatment is costly, has limited efficacy, and severe side effects. To study the dynamic interplay between virus and host in HCV infection, we developed a systems level mathematical model of intracellular HCV replication. We have acquired time resolved measurements of strand-specific RNA and viral protein concentrations in Huh-7 cells. We then set up a mathematical model describing the intracellular replication kinetics, based on mass action kinetics. Our model considers viral polyprotein translation, cleavage, the formation of intracellular replication vesicles (RV) induced by the virus, in which further replication occurs, and export of newly produced viral RNA from the RVs, which can then re-enter the replicative cycle. We particularly focused on the dynamics of the vesicles, their role for viral replication, and involvement of host proteins. Fitting our model to the experimental data, we could show that the model captures the highly dynamic initial events as well as the steady state of viral replication. Results furthermore show that the participation of host proteins is an essential factor in vesicle formation, and that HCV fails to replicate successfully without the protection inside the replication vesicles. This is the first time the initial dynamics of HCV replication has been modeled based on time resolved data. Our model may thus provide the basis to better understand the highly dynamic initial steps after infection.

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