Genetic Studies of Hepatitis C virus Infection and Replication

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Hepatitis C virus (HCV) infection poses a major global health problem by affecting approximately 4 million people in the U.S. and 170 million people worldwide. The majority (75-85%) of individuals with HCV infection develop chronic hepatitis, which leads to cirrhosis (10-20%) and hepatocellular carcinoma (1-5%). Currently, interferon and ribavirin combination therapy is the only option for clinical management of hepatitis C but its clinical benefit suffers from suboptimal efficacy and severe unwanted side effects. Thus, there is an urgent need to discover and develop more efficacious and safer antiviral drugs and vaccines for controlling HCV infection. HCV is an enveloped RNA virus containing a single positive-stranded RNA genome of approximately 9.6 kb in length. The viral RNA genome is composed of a single open reading frame (ORF), flanked by untranslated regions at both the 5’- (5’ UTR) and 3’-ends (3’UTR). Over the years, we have developed robust reverse genetics systems (HCV replicon and infectious virus) that allow genetic analysis of HCV replication in cell culture. HCV RNA replication is an orchestrated biological process occurring in a membrane-bound multiprotein replication complex consisting of viral and cellular proteins acting through protein-protein and protein-RNA interactions. We and others have demonstrated that the highly conserved 5’ and 3’UTRs and the core- and NS5B-coding regions contain cis-acting RNA elements important for HCV RNA replication. Additionally, we found that the functions of HCV nonstructural (NS) proteins can be modulated by viral and cellular proteins through specific protein-protein interactions. We have also demonstrated that HCV RNA is efficiently replicated in mouse cells (MEF and hepatocytes), providing a foundation for development of transgenic mouse models of HCV infection and replication. Furthermore, we have recently discovered that HCV is assembled as apolipoprotein E (apoE)-enriched particles and that apoE is required for HCV infectivity and virion assembly, as demonstrated by siRNA-mediated knockdown of apoE expression and inhibitors of microsomal triglyceride transport protein (MTP). More recently, we have discovered that HCV NS proteins also play important roles in HCV virion assembly. These advances will lead to a thorough understanding of the molecular mechanisms of HCV infection and replication and will facilitate discovery and development of more specific and safer antiviral drugs against HCV.