Hepatitis C virus (HCV) is a member of the Hepacivirus genus of the Flaviviridae family of viruses. HCV possesses a positive-sense, single-stranded RNA genome of ~9600 nucleotides contained within an enveloped virion ~50 nm in diameter. Chronic liver disease caused by HCV infection, including cirrhosis and hepatocellular carcinoma, is a major global problem. An estimated 120–180 million of the world’s population are infected with HCV. Unlike HBV, there is not yet an effective vaccine against HCV. Present therapy for HCV infection, a combination of pegylated interferon (IFN)-α and ribavirin, shows response rates of 40–80%, depending upon HCV genotype.

Much has been learned about how HCV multiplies as well as the means of transmission of the virus (1, 2). The main features of the hepatitis C multiplication cycle are summarized in the schematic in Fig. 1. The virion envelope includes two viral glycoproteins, E1 and E2. Following binding to cellular receptors, virion entry into liver cells occurs by endocytosis with the release of the nucleocapsid into the cytoplasm, where multiplication occurs. The uncoated genome possesses RNA structure elements important for translation and RNA replication. Translation initiation by an internal ribosome entry site mechanism produces an ~3000-amino acid precursor polyprotein that is cleaved by viral and cellular proteases. Among the mature viral protein products generated are structural protein components of virions and several non-structural (NS) proteins found in infected cells. The NS3–NS5B protein coding region includes viral protease, helicase, and polymerase activities and additional proteins that, together with cellular factors, are required for viral RNA replication. Assembly of progeny virions occurs on intracellular membranes, and following their release to the plasma, they may become associated with low density and very low density lipoproteins.

Studies utilizing HCV replicon systems pioneered by Barten-schlag and co-workers provided considerable understanding of the mechanism of HCV RNA replication, and the structural and biochemical insights gained were reviewed in The Journal of Biological Chemistry in 2006 (3). Subsequent development of a cell culture system that permitted complete replication of HCV provided a framework to delineate in biochemical terms the processes involved in initiation of infection, i.e. virion attachment and entry, a topic reviewed by von Hahn and Rice in The Journal of Biological Chemistry in 2008 (4). Now, three additional minireviews on HCV summarize important new findings about the virus and its interaction with the host. The first minireview in this series concerns the structure of NS3 and the functional roles of the novel multifunctional HCV protein that possesses two enzymatic activities, protease activity and helicase activity (5). The second minireview summarizes recent insights gained about the trafficking of HCV proteins and the process of assembly of progeny virions and their subsequent release from HCV-infected cells (6). The third minireview focuses on the host’s innate immune response to HCV infection and the multiple strategies utilized by HCV to evade innate antiviral responses (7).

In the first minireview, Kevin D. Raney, Suresh D. Sharma, Ibrahim M. Moustafa, and Craig E. Cameron at The Pennsylvania State University and University of Arkansas for Medical Sciences, in their article entitled “Hepatitis C Virus Non-structural Protein 3 (HCV NS3): A Multifunctional Antiviral Target,” consider new developments in both the biochemistry and structural biology of the bifunctional NS3 protein (5). NS3 possesses in the N-terminal region a serine protease activity and in the C-terminal region an RNA helicase activity. The structure, substrate recognition, and mechanism of the NS3 protease, which processes the NS region of the HCV polyprotein, and the NS3 helicase that unwinds RNA and DNA substrates are considered as well as NS3 as a therapeutic target.

The second minireview of the series, by Daniel M. Jones and John McLaughlan at the Medical Research Council Virology Unit in Glasgow, UK, entitled “Hepatitis C Virus: Assembly and Release of Virus Particles,” summarizes progress in understanding HCV protein trafficking and virion assembly and release (6). The stages of assembly and egress of infectious HCV particles at specialized sites on the endoplasmic reticulum (ER) membrane are considered in biochemical terms, beginning with an initial phase of virion assembly with core-coated lipid droplets on the cytosolic side of the ER membrane, maturation in the ER lumen, and then release and the role that pathways involved in the release of lipoproteins from hepatocytes play in the process.

The third minireview, by Stanley M. Lemon at The University of North Carolina at Chapel Hill, entitled “Induction
and Evasion of Innate Antiviral Responses to Hepatitis C Virus,” summarizes progress in understanding the cellular signaling pathways and antiviral responses antagonized by HCV proteins (7). The cytoplasmic RIG-I sensor and the endosomal TLR3 sensor detect viral RNA to trigger innate antiviral responses that include IRF3 activation and IFN synthesis. Both pathways are antagonized by HCV, including by NS3-mediated cleavage of their respective adaptor proteins. Also considered are examples of impairment of IFN-induced signaling and of the activities of IFN-induced gene products, including the PKR kinase. The balance between activation and antagonism of the innate antiviral response influences subsequent adaptive responses and hence is an important contributor to the outcome of the HCV-host interaction.

REFERENCES


FIGURE 1. Schematic diagram of the HCV multiplication cycle. Enveloped HCV virion particles are depicted as spheres, and in the plasma, they can be associated with cellular lipoproteins (low density (LDL) and very low density (VLDL) lipoproteins). Following virus entry, most probably by E2 binding and receptor-mediated endocytosis, uncoating results in the release of the positive-sense, single-stranded RNA (ssRNA) genome. The 5′-untranslated region includes an internal ribosome entry site (IRES) that directs 5′-cap-independent synthesis of a polyprotein of ~3000 amino acids (aa) that undergoes processing by viral and cellular proteases. Ten mature viral proteins are produced, some structural (capsid core C (Cc a) and envelope glycoproteins E1 (E1 gp) and E2 (E2 gp)) and others non-structural (p7 membrane protein (p7 mp), NS2 protease (NS2 pr), NS3 protease and helicase (NS3 pr hc)), NS4A cofactor (4A cf) for NS3, NS4B membrane protein (4B mp), NS5A phosphoprotein (5A pp), and NS5B RNA-dependent RNA polymerase (5B pol)). In addition to its role as mRNA, the positive-sense RNA genome also serves as the template for RNA replication catalyzed by the viral RNA-dependent RNA polymerase (NS5B) that occurs in association with the ER membrane. Other components of the HCV replication complex include both viral proteins and cellular factors. The complementary minus-sense RNA produced then serves as the template for synthesis of positive-sense RNA that fulfills three functions, mRNA for translation, template for RNA replication, and progeny genome that undergoes encapsidation into new virions. This figure was adapted from Ref. 2 with permission. SR-B, scavenger receptor class B; miR122, microRNA-122.