

Minireview Prologue

**ELUCIDATING HEPATITIS C VIRUS – HOST INTERACTIONS AT THE
BIOCHEMICAL LEVEL**

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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 (1). Chronic liver disease caused by HCV infection, including cirrhosis and hepatocellular carcinoma, is a major global problem. An estimated 120 million to 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 alpha 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 by the Figure 1 schematic. 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 by an internal ribosome entry site mechanism produces a ~3,000 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 to 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 LDL and VLDL lipoproteins.

Studies utilizing HCV replicon systems pioneered by Bartenschlager and his colleagues provided considerable understanding of the mechanism of HCV RNA replication, and the structural and biochemical insights gained were reviewed in *The JBC* in 2006 (3). Subsequent development of a cell-culture system that permitted complete replication of hepatitis C virus provided a framework to delineate in biochemical terms the processes involved in initiation of infection, that is, virion attachment and entry, a topic reviewed by von Hahn and Rice in *The JBC* 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 issue concerns the structure of NS3 and the functional roles of the novel multifunctional HCV protein that possesses two enzymic 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 Rainey, Suresh Sharma, Ibrahim Moustafa and Craig Cameron at Pennsylvania State University and the University of Arkansas, 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 Jones and John Mclauchlan at the Medical Research Council Institute of Virology, in Glasgow, U.K., 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 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 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 interferon 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.

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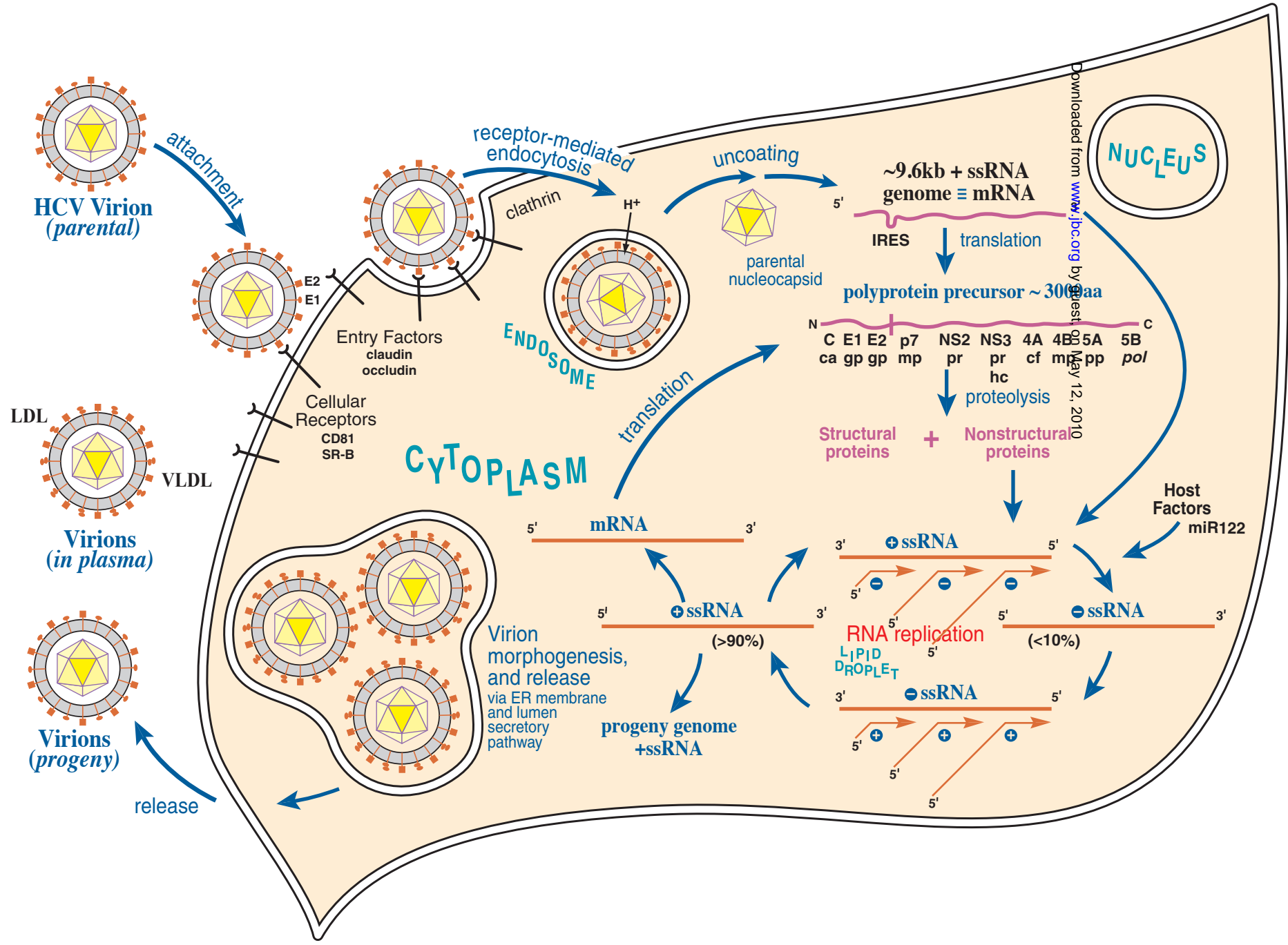
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FOOTNOTES

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FIGURE LEGENDS

FIGURE 1. Schematic diagram of the hepatitis C virus multiplication cycle. Enveloped HCV virion particles are depicted as spheres, and, in the plasma, they can be associated with cellular lipoproteins (LDL, VLDL). Following virus entry, most probably by E2 binding and receptor-mediated endocytosis, uncoating results in the release of the positive-sense single-stranded RNA genome. The 5'-untranslated region includes an internal ribosome entry site (IRES) that directs 5'-cap-independent synthesis of a polyprotein of ~3,000 amino acids that undergoes processing by viral and cellular proteases. Ten mature viral proteins are produced, some structural (capsid core C; envelope glycoproteins E1 and E2) and others nonstructural (p7 membrane protein; NS2 protease; NS3 protease and helicase; NS4A cofactor for NS3; NS4B membrane protein; NS5A phosphoprotein; NS5B RNA-dependent RNA polymerase). In addition to its role as mRNA, the positive-sense genome RNA 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. Adapted from Samuel 2006 with permission.



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