Virus-host Interactions during Hepatitis C Virus Entry - Implications for Pathogenesis and Novel Treatment Approaches

Joachim Lupberger1, Mirjam B. Zeisel1, Anita Haberstroh3, Eva K. Schnober3, Sophie Krieger1, Eric Soulier1, Christine Thumann1, Cathy Royer1, Samira Fafi-Kremer1, Catherine Schuster1, Françoise Stoll-Keller1, Hubert E. Blum3 and Thomas F. Baumert1,2,3**

(1. Inserm, U748, Hôpitaux Universitaires de Strasbourg, Université Louis Pasteur, 3 Rue Koeberle, F-67000 Strasbourg, France; 2. Service d’Hépatogastroentérologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; 3. Department of Medicine II, University of Freiburg, Germany)

Abstract: Hepatitis C virus (HCV) is a member of the Flaviviridae family and causes acute and chronic hepatitis. Chronic HCV infection may result in severe liver damage including liver cirrhosis and hepatocellular carcinoma. The liver is the primary target organ of HCV, and the hepatocyte is its primary target cell. Attachment of the virus to the cell surface followed by viral entry is the first step in a cascade of interactions between the virus and the target cell that is required for successful entry into the cell and initiation of infection. This step is an important determinant of tissue tropism and pathogenesis; it thus represents a major target for antiviral host cell responses, such as antibody-mediated virus neutralization. Following the development of novel cell culture models for HCV infection our understanding of the HCV entry process and mechanisms of virus neutralization has been markedly advanced. In this review we summarize recent developments in the molecular biology of viral entry and its impact on pathogenesis of HCV infection, development of novel preventive and therapeutic antiviral strategies.

Key words: Hepatitis C virus; Viral entry; Entry inhibitor; Neutralizing antibodies

VIRAL AND CELLULAR DETERMINANTS OF VIRAL ENTRY

Hepatitis C virus (HCV) is a member of the Flaviviridae family and causes acute and chronic hepatitis. A persistent HCV infection may result in severe liver damage including liver cirrhosis and hepatocellular carcinoma (17). HCV infects only humans and chimpanzees (33). The liver is the primary target organ of HCV, and the hepatocyte is its primary target cell. Attachment of the virus to the cell surface followed by viral entry is the first step in a cascade of interactions between the virus and the target cell that is required for successful entry into the cell and initiation of infection (Fig. 1) (35). This step is an important determinant of tissue tropism and pathogenesis; it thus represents a major target for antiviral host cell responses, such as antibody-mediated virus neutralization, and antiviral therapy (for review see also (56)).
Viral determinant of viral entry: envelope glycoproteins

The HCV genome encodes a single precursor polyprotein of about 3,000 amino acids that is cleaved co- and post-translationally into functional structural and non-structural proteins by host and viral proteases including two envelope glycoproteins, E1 and E2. In analogy to other members of the Flaviviridae family, the HCV capsid complexes the viral RNA genome and is thought to adopt a classical icosahedral scaffold in which the two envelope glycoproteins E1 and E2 are anchored to the host cell-derived double-layer lipid envelope (38). E1 and E2 are type I transmembrane glycoproteins containing up to 6 and 11 potential glycosylation sites, respectively and forming noncovalent heterodimers.

Studies of infectious HCV life cycle have been limited by the lack of an efficient cell culture system. Several model systems have thus been developed for the study of defined aspects of the HCV life cycle such as viral entry, replication, assembly and release (for review see (5)). Recombinant HCV envelope glycoproteins (40), HCV-like particles (HCV-LPs) (4, 13, 53) and retroviral HCV pseudotypes (HCVpp) (10, 24) have been successfully used to analyze virus attachment and entry. Most recently, efficient in vitro model systems for the production of infectious recombinant virions (HCVcc) have been described (32, 60, 52). Using these model systems, it could be demonstrated that envelope glycoproteins E1 and E2 are critical for host cell entry.

Host entry factors for HCV infection

Using various model systems for HCV-host interaction, several host entry factors have been iden-