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EDITORIAL

Heterogeneity of Hepatitis C Virus Particles and Their Evolution During Infection

Hepatitis C virus (HCV) was identified by molecular cloning of its RNA genome after conventional methods of virus identification failed. This failure was due to both low levels of HCV particles in the blood of infected patients and particle heterogeneity. HCV is a highly variable virus. In addition to 6 genotypes and more than 60 subtypes, HCV mutants circulate in the blood as millions of quasispecies, many of which are able to escape host immune responses and even direct-acting antiviral (DAA) therapy.

HCV heterogeneity is also due to the association of virus particles with lipoproteins. Indeed, a peculiarity of HCV is its interaction with hepatic lipid metabolic pathways at all stages of its life cycle. Viral particles are associated with very low-density (VLDL) and low-density lipoproteins, which play a critical role in HCV cell entry (via lipoprotein receptors); morphogenesis and the release of infectious virus particles depend on VLDL synthesis and export pathways. The HCV virion (lipo-viro particle [LVP])[1] is composed of nucleocapsid and E1E2 envelope glycoproteins, liver cell–derived triglyceride-rich lipoproteins (TRLs), cholesterol, and several apolipoproteins (ApoE, ApoB-100, ApoCI, ApoCII, ApoCIII).[2] The lipid components of the virus determine its size (40–70 nm), buoyant density, hepatotropism and infectivity, morphogenesis, and maturation of virus particles. Lipoproteins and ApoE facilitate viral escape from neutralizing antibodies.[3] Noninfectious forms of HCV in the blood include nucleocapsid-free lipoprotein-like particles[4] and nonenveloped nucleocapsids.[5]

HCV particles in the blood vary in size and in content of lipids and apolipoproteins. The concentration and properties of virus particles depend on the stage of infection (acute or chronic)[6] and fluctuate with postprandial lipemia.[7] Both the lipoprotein composition of virus particles and serum lipid profiles might influence a patient's susceptibility to infection.[8]

HCV displays a species and tissue specificity limited to the human hepatocyte, but the density and infectivity of HCV particles depend on the specific type of cell in which the virus is produced. Huh7 hepatoma cells, used to culture HCV in vitro, have deficient lipoprotein metabolism and produce immature VLDLs. Consequently, culture-derived HCV has a different lipid composition, higher density, and lower infectivity than virus strains produced in chimpanzees or in the humanized mouse models.[9]

Serum-derived HCV is difficult to grow *in vitro*. Thus, development of uPA-SCID mouse model with transplanted human primary hepatocytes enabled production of viruses with the appropriate lipid composition for studies of HCV receptors and evaluation of antivirals.[10] Nevertheless, more robust chimeric human-liver mice models are still needed for investigation of the complex virus-lipid interactions during infection.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology,* Andréo et al[11] used fah−/− mice transplanted with human primary hepatocytes to analyze the biophysical properties and infectivity of HCV particles in the blood and their evolution over the course of infection. Chimeric mice exhibited human-like lipoprotein profiles and were shown to be suitable for studies of lipoprotein-associated HCV. Two major viral populations (banding at densities of 1.1 and 1.15–1.19 g/mL) were detected in fractionated blood of J6/JFH1 strain infected mice, with higher infectivity for the low-density population, similar to the results reported for J6/JFH1 infected uPA-SCID mice and chimpanzees.[9,12] The lower-density virus peak probably contained lipoprotein-like particles in addition to infectious LVPs.[4] The third peak (density >1.3 g/mL) detected in some sera might represent a virus fraction less enriched in lipoproteins or nonenveloped nucleocapsids.[5] The proportions of virus populations varied during the course of infection, with an increasing predominance of high-density particles and general decrease of infectivity reflecting changes in biochemical features of the virus. Sucrose feeding influenced the density and infectivity of virus particles that correlated with redistribution of triglycerides and cholesterol among lipoproteins.

This study confirms that virus-associated lipid components modulate the biophysical properties and infectivity of HCV particles. It also shows that viral populations evolve over time and suggests that metabolic changes influence the course of infection. These results are in accordance with observations that alimentary lipemia alters the density and dynamics of viral populations in HCV-infected patients because of modulation of TRL metabolism.[7]

Evolution of the biochemical features of the virus during infection is a fascinating aspect of structural HCV heterogeneity related to several mechanisms: VLDL-dependent morphogenesis and release of virus particles, ApoE-dependent virus maturation,[13] and intravascular remodeling of HCV-associated lipoproteins. Further studies in models that reflect these aspects of infection *in vivo* would help to develop novel host-lipid targeting inhibitors to improve existing DAA therapies.

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Conflicts of interest
The author discloses no conflicts.

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