

Hepatitis C virus, alcohol and lipid droplets

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Hepatitis C virus (HCV) persistence drives the progression of HCV infection. This progression is usually asymptomatic in HCV-infected patients. For many years, clinical manifestations of HCV persistence are restricted to fatty liver followed by slow development of fibrosis, cirrhosis and hepatocellular carcinoma [1, 2]. Thus, HCV persistence is a “first hit” triggering HCV pathogenesis. There are “second hits” that stabilize the infection and cause faster progression, exacerbation of pathological features of HCV infection and poor response to anti-viral therapy. One of these “second hits” known to affect HCV pathogenesis is alcohol. Liver steatosis is common for both HCV infection and alcohol and is considered as a co-factor in development and progression of fibrosis.

Hepatitis C virus is an RNA virus packaged into an enveloped virus particle. HCV polyprotein has 3000 amino acids and is co-translational and posttranslational processed by cellular and viral proteases to form three structural proteins (core, E1 and E2), an ion channel protein (p7) and six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B) [3]. Viral RNA replication requires the formation of a membrane-associated replication complex composed on HCV non-structural proteins, RNA and cellular membranes. Enveloped HCV virions carrying a newly synthesized viral genome are formed by budding into the endoplasmic reticulum lumen and leave the cells through the secretory trans-Golgi pathway [4].

Lipid Droplets and Infectious HCV Formation

Structural proteins are released from polyprotein by host signal peptidase. Core protein is further processed by signal peptide peptidase to mature core, and this cleavage promotes the transport of core from the endoplasmic reticulum to the surface of lipid droplets (LD), where the full infectious particle is assembled [5]. In HCV+ cells, core protein is usually detected on the endoplasmic reticulum membrane and at the surface of LD. Core protein encapsulates newly synthesized HCV RNA and by interacting with two surface proteins, E1 and E2, buds into endoplasmic reticulum lumen [6]. The exact mechanism of recruitment of core protein to LDs is not clear. It has been shown that trafficking of core to LD involves Rab18 and that knockdown of Rab18 reduces HCV infectivity [7]. The localization of HCV core protein to LD depends on host diacylglycerol acyltransferase 1 (DGAT1), the enzyme that synthesizes triglycerides in endoplasmic reticulum lumen. The abrogation of DGAT1 causes severe impairment in HCV entry [8, 9], and this protein plays a pivotal role in translocation and attachment of core protein to LD, which is crucial for HCV assembly process.

Hepatitis C virus core protein is a key factor in the regulation of LD accumulation. First, it activates SREBP-1C and RXR- α necessary for lipid biosynthesis [10]. In addition, core protein blocks VLDL secretion by inhibiting microsomal triglyceride transfer protein activity [11] and by induction of peroxidation of lipids and proteins involved in VLDL secretion [12]. Recently, it has been reported that core at the surface of LDs interferes with the activity of adipose triglyceride lipase (ATGL), the key lipolytic enzyme in the first step of triglyceride breakdown, thereby blocking lipolysis [13]. Furthermore, modulation of triglyceride and cholesterol ester synthesis impairs assembly of virus on LDs [14]. Interestingly, there is no difference in the localization of core protein to LDs between HCV genotype 3 (that causes the most severe steatosis) and other HCV genotypes, but genotype 3 induces the largest size of LDs [15, 16]. HCV core-coated LDs accumulate in the perinuclear region due to expression of core protein's lipid binding domain II (DII-

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Received: 09 January 2015

Published: 24 January 2015

core) that slows down LD speed and finally, enhances viral infectivity [17].

Lipid droplets is directly involved in the production of infectious HCV particles. The unique membranous structures (“membranous” web) are detected around the LDs in HCV-producing cells, and significant amount of NS5A protein and HCV RNA are recruited to these LDs. However, the disruption of core protein association with LDs causes a defect in association of NS5A protein and HCV RNA and blocks the virus assembly [10], indicating that the attachment of core protein to LDs recruits non-structural protein and replication complexes to LD-associated membranes. The attachment of non-structural HCV proteins and recruitment of replication complex is orchestrated by HCV protein NS2 by induction of multiple protein-protein interactions. Moreover, NS2 acts to coordinate virus assembly by mediating interactions between envelope proteins and NS3 and NS5A within replication complexes adjacent to LDs, where virus particle assembly is thought to occur [18]. Thus, the role of LDs in the production of infectious HCV particles includes several aspects: HCV replication complex and non-structural proteins are aggregated on LDs. This provides a factor required for infectivity to the virus particle and incorporates virus particle into a vesicle transport system of lipid or lipid-related material to export out of the cells [19].

To our knowledge, there are no published studies on the role of ethanol on LD-associated HCV assembly. We observed a sufficient accumulation of LDs in livers of HCV ethanol-fed core-transgenic mice (unpublished observations) and to lesser extent, in the livers of ethanol-fed NS5A+ mice [20]. Also, in Huh7.5-CYP cells, ethanol and acetaldehyde exposure enhanced amount of LDs, but impaired an expression of core protein on LDs as well as infectivity of cell supernatants. However, the mechanisms of these events are not clear yet, and they remain to be one of uninvestigated, but important areas of HCV-ethanol studies, which are attributed to alcohol-induced progression of liver injury in HCV-infection.

How to cite this article

Osna N. Hepatitis C virus, alcohol and lipid droplets.
Int J Hepatobiliary Pancreat Dis 2015;5:1–3.

Article ID: 100026IJHPDNO2015

doi:10.5348/ijhpd-2015-26-ED-1

Author Contributions

Natalia Osna – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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