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TOPIC HIGHLIGHT

2015 Advances in Hepatitis C virus

Modulation of host lipid metabolism by hepatitis C virus: Role of new therapies

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Abstract

It is well established that hepatitis C virus (HCV) infection and replication relies on host lipid metabolism. HCV proteins interact and associate with lipid droplets to facilitate virion assembly and production. Besides, circulating infective particles are associated with very low-density lipoprotein. On the other hand, higher serum lipid levels have been associated with sustained viral response to pegylated interferon and ribavirin therapy in chronic HCV infection, suggesting a relevant role in viral clearance for host proteins. Host and viral genetic factors play an essential role in chronic infection. Lipid metabolism is hijacked by viral infection and could determine the success of viral replication. Recently development of direct acting antiviral agents has shown a very high efficacy (> 90%) in sustained viral response rates even for cirrhotic patients and most of the viral genotypes. HCV RNA clearance induced by Sofosbuvir has been associated with an increased concentration and size of the low-density lipoprotein particles. In this review, host genetic factors, viral factors and the interaction between them will be depicted to clarify the major issues involved in viral infection and lipid metabolism.

Key words: Hepatitis C virus; Lipid metabolism; Direct acting antiviral agents; Genetic interaction; Sofosbuvir

Core tip: Hepatitis C virus (HCV) is known to be closely related and associated with host lipid metabolism. Recently development of direct acting antiviral agents has shown a very high efficacy (> 90%) in sustained viral response rates even for cirrhotic patients and most of the viral genotypes. HCV RNA clearance induced by Sofosbuvir has been associated with an increased concentration and size of the low-density lipoprotein particles. Host and viral genetic factors play an essential role in chronic infection. Lipid metabolism is hijacked by viral infection and could determine the success of viral replication.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a relevant public health problem, infecting approximately 170 million people worldwide[1]. About 70% of infected patients will develop chronic HCV infection. One third of them have a significant increased risk of advanced liver fibrosis, cirrhosis development and finally, hepatocellular carcinoma. With the recent emergence of first generation direct acting antivirals (DAAs), and the development of a second generation DAAs, They have been a near-final step towards the eradication of HCV infection[2-5].

HCV is known to be closely related and associated with host lipid metabolism. HCV proteins interact and associate with lipid droplets to facilitate virion assembly and production[6]. Besides, circulating infective particles are associated with very low-density lipoprotein (VLDL)-like particles, referred as lipoviral particles (LVP)[7]. A proposed mechanism to facilitate HCV entry has been postulated based on the incorporation of host apolipoproteins into the LVP[7-9]. It has been shown that several apolipoproteins are necessary for viral assembly and the production of infective particles[10-12]. Moreover, elevated serum lipid levels have been associated with the rate of sustained viral response to pegylated interferon and ribavirin (Peg-IFN + RBV) therapy for chronic HCV infected patients, suggesting a key role for host proteins in the eradication of viral infection[13,14]. In this review, host genetic factors, viral factors and the interaction between them will be depicted to clarify the major issues involved in viral infection and lipid metabolism.

HOST GENETIC FACTORS

All viruses, as obligate intracellular parasites, are implicitly dependent on host cell functions for their survival and propagation. There is an emerging understanding of the possible role played by lipid droplets (LDs) in the life cycle of a growing number of viruses, including HCV[15,16]. In the establishment of HCV infection, LDs occupy a central role in the generation of infectious virions and are specifically targeted by viral proteins for this purpose[17]. Diacylglycerol acyltransferase-1 (DGAT1) catalyses the final stage in triglyceride synthesis, and also plays a central role in formation of LDs. It has been shown that DGAT1 interacts with both core and NS5A to facilitate their recruitment to LDs[18]. DGAT1 also appears to facilitate interaction between core and NS5A, thereby functioning as a molecular bridge between the two proteins to ensure that they are targeted to the same LD[19].

The close relationship between serum LDL-cholesterol (LDL-C) concentration and the chance of achieving sustained viral response has been reported largely in patients under Peg-IFN + RBV therapy[20] as well as with direct-acting antiviral-based triple therapy[21]. Lipid-conforming LVPs are released after HCV eradication, thus increasing concentration can be found in plasma and their concentrations increase in plasma. As previously pointed out, the higher the baseline LDL-C serum level, the greater the chance of curing hepatitis C. This finding is especially relevant in patients in patients bearing non-favourable IL28B genotype, together with previous non-responders patients to Peg-IFN + RBV when treated with triple therapy using telaprevir[22]. Some works have analyzed several genes implicated in lipid transport, such as *APOB*, *APOC-Ⅲ*, *APO-L3*, and lipid-signaling leptin receptor, MTTP together with liver X receptor/retinoid X receptor pathways. Several changes in these genes have corroborated the link between HCV infection and lipid metabolism and could also identify these genes as therapeutic targets for HCV infection, like FASN inhibition or DGAT activity blockage for inhibition of viral particles production, together with the prevention of the viral entry in the cell[23,24] (Figure 1).

The liver is the main organ for lipid homeostasis in the entire body, through production and uptake of lipoproteins. Lipid homeostasis is a complex mechanism that involves a large amount of genes. Several genetic analysis, including Genome-Wide analysis have been performed to shed some light on this process. This type of analysis has identified a strong association between single nucleotide polymorphisms (SNPs) near the *IL28B* locus and the chance of achieving sustained virologic response (SVR) to Peg-IFN + RBV therapy in HCV patients, as well as spontaneous viral clearance[25,26]. Moreover, higher plasma levels of ApoB have been associated with sustained virological response in HCV patients bearing the rs8099917 responder genotype (located proximal to rs12979860) in the *IL28B* gene[27]. Besides, Duggal *et al*[28] described the association of SNP rs4273729 related to the HLA class Ⅱ genes on Chromosome 6 with spontaneous HCV clearance independently of *IL28B* genotype. Nowadays, the role of the *IL28B* genotype on SVR is attenuated - non significant - in the setting new therapies with NS3 protease, NS5A or NS5B polymerase inhibitors.

Adiponutrin or patatin-like phospholipase domain containing 3 (*PNPLA3*) is a member of the patatin-like phospholipase family. It is expressed in several human tissues with highest expression in the liver[29]. *PNPLA3* acts as a transacylase, which synthesises intracellular triglycerides by transferring acyl groups from monoglycerides to mono- and diglycerides[30]. A study by Trépo *et al*[31] found, in Caucasian chronic hepatitis C (CHC) patients, a strong and independent association between *PNPLA3* and liver damage. Patients with

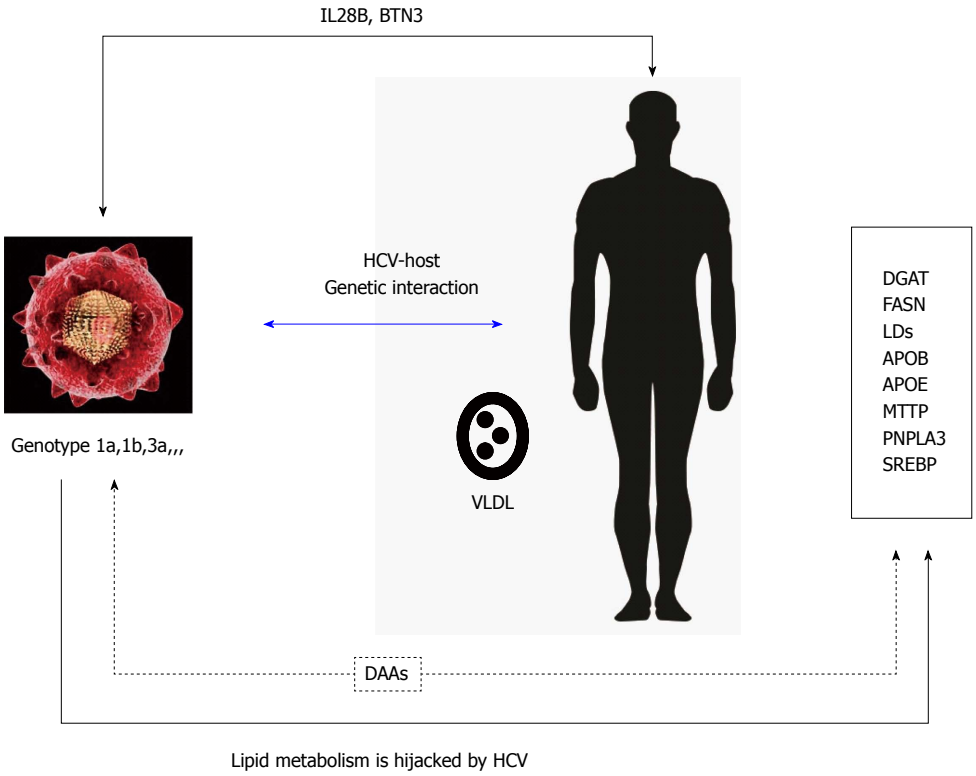

Figure 1 Schematic representation of hepatitis C virus and host interplay during hepatitis C virus infection. Viral infection has a direct effect on lipid metabolism through two main mechanisms: first, by deregulating gene expression (*FASN, DGAT, MTTP, SREBP*). This effect can be modulated by certain SNPs in PNPLA3, among others. Secondly, VLDL synthesis is affected, since HCV replication takes place on lipid droplets. SNPs: Single nucleotide polymorphisms; VLDL: Very low-density lipoprotein; HCV: Hepatitis C virus; DGAT: Diacylglycerol acyltransferase; LD: Lipid droplet; PNPLA3: patatin-like phospholipase domain containing 3.

homozygosity of the risk allele had a 2.5-fold higher risk for hepatic steatosis and an over three-fold higher risk for fibrosis as well as for fibrosis progression.

HCV interacts with several proteins of the VLDL secretion pathway for the production of infectious particles. Circulating LVP in an infected patient indicate that HCV virions are associated with hepatically derived triglyceride-rich lipoproteins (TRL) containing apoB-100. These lipo-viro-particles are also associated with gut related lipoproteins containing apoB[8,32]. HCV infection also leads to TRL accumulation through transcriptional activation of lipogenic genes, thus stimulating synthesis of lipids in patients[33]. Besides, several studies on HCV patients have indicated that the virus induced lipogenic genes over-expression. This process may exert a strong influence on inflammation and fibrosis progression in HCV patients, rather than causing the lipid accumulation observed in hepatic steatosis[34].

ApoE plays a relevant role in the assembly and production of viral particles during HCV infection. ApoE depletion has a significant effect in HCV particles production compared to apoB or apoA1 in the same model. This effect may be related to the role of apoE in HCV assembly and interaction with the viral protease NS5A, as previously described[11,12,35]. The interplay NS5A-apoE is a key factor for the building of the viral assembly machinery.

VIRAL FACTORS

A previous work performed by our group demonstrated a relationship between *IL28B* polymorphism and lipid profile in patients with hepatitis C genotype 1[20]. This association was not present in patients with hepatitis C genotype 3 or 4 and in the non-infected control group. LDL and total cholesterol levels were higher in patients infected with *HCV* genotypes 1 and 4 harbouring the favourable (CC) genotype for *IL28B* gene. HCV directly causes the appearance of large lipid droplets in hepatocytes. Remarkably, HCV replication rates are higher in patients infected with genotype 3, concomitant with more frequent and severe hepatic steatosis[36]. In addition, HCV-induced steatosis related to genotype 3 infections is abolished when antiviral therapy is achieved. Moreover, studies performed *in vitro*, where cells are transfected with HCV core protein from different genotypes show that core protein is sufficient for lipid droplets induction in the hepatocytes, which is especially relevant - more efficient - in the case of genotype 3a core protein[37]. Lack of understanding for these mechanisms still hamper the characterizarion of these processes, including the appearance of very large lipid droplets in genotype 3. The reasons to explain why genotype 3 is more efficient in steatosis development are still unknown, since very limited studies have been performed using different genotypes

in the same model[38].

HCV (including genotype 3a) has been reported to activate *in vitro* the sterol regulatory element binding proteins 1c and 2, two transcription factors involved in the control of neolipogenesis[39]. However, the evidence obtained in patients with different viral genotypes is inconclusive[34,40] and thus it is unclear whether steatosis in genotype 3 is favoured by an increased fatty acid and/or cholesterol synthesis.

HOST-VIRAL INTERACTIONS AND LIPIDS

HCV belongs to the *Flaviviridae* family. These viruses use the secretory pathway of the cell for their way out. Lipoprotein metabolism is tightly associated to the secretory pathway. For this reason, it has been suggested that in HCV infection, the virus uses for its own benefit the VLDL synthesis mechanism of the host cell. Based on an extensive siRNA analysis, it has been shown that most of the host proteins involved in HCV secretion belongs to the classical trafficking pathway, including microtubules, Golgi recycling endosomes, VAMP1 secretory vesicles and the lipoprotein apoE, which is linked to the core protein in the trafficking pathway[41].

High frequency of chronic infection reflects the fact that HCV has evolved several mechanisms to evade and suppress innate immunity, resulting in HCV progression to chronicity[42]. The viral NS3/4A protease is a central component of the HCV innate immune evasion strategy. The multifunctional NS3/4A protease is required for HCV replication, during which it processes the HCV polyprotein at several sites to liberate the viral NS proteins[43]. NS3/4A also targets and cleaves mitochondrial antiviral signaling protein (MAVS) from intracellular membranes to prevent signal transduction[44,45] thus, MAVS cleavage by the HCV NS3/4A protease disrupts RIG-I signaling of innate antiviral immunity and attenuates IFN production[46].

The interaction host-virus resulted on clone selection, immune response modulation and induction/inhibition of proteins involved in the viral entry into the hepatocyte. Recent insights into how HCV regulates innate immune signaling within the liver reveal a complex interaction of patient genetic background with viral and host factors of innate immune triggering and control that imparts the outcome of HCV infection and immunity[47]. Host immune responses, both innate[48] and adaptive[49] together with factors regulating HCV entry into the cell and viral quasispecies, have been explored[50]. In a previous analysis, we identified BTN3A2 (rs9104) to be associated with the selection of viral genotype[51]. Our group is currently exploring HCV susceptibility and to determine the influence of butyrophilin (BTN) family on the selection of HCV genotype. An association between BTN3A2 SNP rs9104 and HCV infection by genotype 1 has been recently described, where genetic variants play a relevant role in selecting a HCV genotype and influencing disease progression[52].

ROLE OF NEW HCV THERAPIES IN LIPID METABOLISM

Sofosbuvir is one of the most relevant drugs for hepatitis C therapy. It is a nucleotide analogue inhibitor of the NS5B polymerase which has been recently approved by the Food and Drug Administration and European Medicines Agency for HCV treatment and is currently used in combination with other antivirals like daclatasvir and ledipasvir (NS5A inhibitors). Other combinations include a protease inhibitor such as simeprevir or even with the formerly defined as Standard of Care for hepatitis C (peg-IFN + RBV). Sofosbuvir has demonstrated a consistently potent antiviral activity across several HCV genotypes, and has been found to be safe and well tolerated, showing a very high efficacy (> 90%) in sustained viral response rates even for cirrhotic patients. HCV RNA clearance induced by Sofosbuvir has been associated with an increased concentration and size of the LDL particles. Recently, Meissner *et al*[53] have demonstrated rapid changes in serum lipoprotein particle concentration during treatment of chronic HCV, genotype 1-infected patients with an IFN-free regimen of SOF and RBV. This likely reflects an altered balance of lipogenesis subsequent to removal of host lipid metabolism perturbation induced by HCV. This fact could be due to differential regulation of genes associated with lipid transport (*APOC3* and *APOL3*) and lipid assembly and signaling (*LEPR* and *MTTP*) that has been observed in patients with paired liver biopsies available for analysis[54,55].

Several studies have suggested that statins [3-hydroxy-3-methylglutaryl CoA reductase (HMG Co-A) inhibitors] that inhibit *de novo* cholesterol synthesis, can block HCV replication[56]. Statins appear to inhibit HCV replication *via* inhibition of geranylgeranylation of a host protein FBL2 which is required for HCV replication[57]. Rao *et al*[58] have demonstrated that statin use was associated with an improved SVR among both diabetic patients and non-diabetic patients receiving combination antiviral therapy. Hence, poor diabetes control leads to a lower SVR rate.

CONCLUSION

Host and viral genetic factors play an essential role in chronic infection. Lipid metabolism is hijacked by viral infection and could determine the success of viral replication. Mechanisms of treatment relapse with DAA therapy are nuclear and differential regulation of host lipid metabolic pathways may be associated with treatment relapse and support further investigation of lipid metabolites as predictors of treatment response

to DAA-therapy.

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