

## Entry of hepatitis C virus into the cell: A therapeutic target

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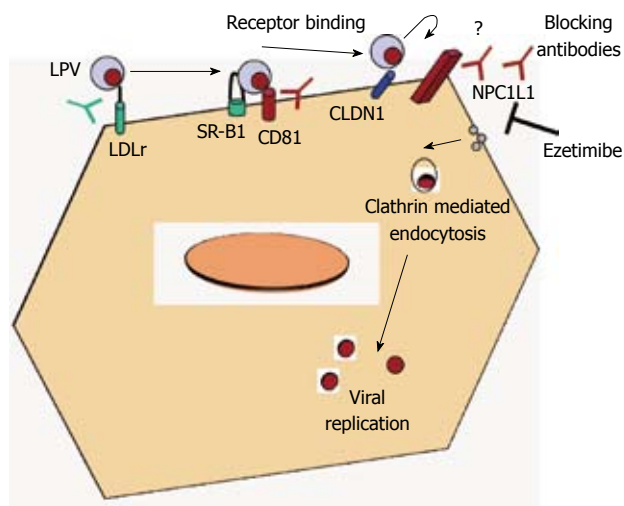
### Abstract

Several receptors have been identified as implicated on viral entry into the hepatocyte; and, this interaction between the virus and potential receptors could modulate infection, spontaneous viral clearance, persistence of the infection and the widespread of the virus as outbreak. Nevertheless, the playing role of each of them remains controversial. The Niemann-Pick type C1 like 1 gene (*NPC1L1*) receptor has been recently implicated on hepatitis C virus (HCV) entry into the cell and ezetimibe, an anti-cholesterol drug seems to block that, emerging the idea to control hepatitis C outbreak modulating lipid-related receptors. Hepatitis C infection seems to modulate lipid metabolism according to host genetic background. Indeed, it circulates like a lipovirparticle. The main aim of this field of vision would be to discuss the role of hepatocyte receptors implicated on virus entry, especially NPC1L1 and the therapeutic options derived from the better knowledge about HCV-lipids- receptors interaction.

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### INVITED COMMENTARY ON HOT ARTICLES

Viral entry is the first step of virus-host cell interactions and, is a highly orchestrated process involving several viral and host cell factors. Indeed, the virus is able to escape from neutralizing antibodies and promote direct cell-cell transmission. Understanding the mechanisms of viral entry and escape is a prerequisite to define the viral and cellular targets that will give broad protection against hepatitis C virus (HCV) infection. HCV is an enveloped single-strand RNA virus that mainly targets hepatocytes. Due to the difficulty to grow HCV *in vitro* and the species specificity of this virus, surrogate model systems have been developed to study HCV entry into hepatocytes: recombinant envelope glycoproteins<sup>[1]</sup>, HCV-like particles<sup>[2]</sup>, HCV pseudo-particles<sup>[3,4]</sup> and recombinant infectious HCV<sup>[5-7]</sup> have been used to study the interactions of the viral envelope with human hepatoma cells or primary human hepatocytes. Four cellular factors have been described as essential for HCV entry (Figure 1): the tetraspanin molecule CD81, the scavenger receptor class B member I and the tight junction proteins claudin-1 and occludin<sup>[8]</sup>. Interestingly, neutralizing antibodies against CD81 are able to block HCV entry *in vitro* and also in im-



**Figure 1** Schematic representation of viral receptors in hepatocytes. Possible mechanisms of viral entry blockade are also depicted by using specific antibodies or inhibitory drugs. LDLr: Low-density lipoprotein receptor; NPC1L1: Niemann-Pick C1-like 1 cholesterol absorption receptor; SR-B1: Scavenger receptor class B type 1; LPV: Lipoviroparticle; CLDN1: Claudin-1.

munodeficient mice transplanted with human hepatocytes, the best currently available small animal model of HCV infection<sup>[9]</sup>. Neutralizing antibodies against the HCV envelope proteins E1 and E2 could also represent a promising approach to avoid HCV infection, but the main challenge here is the enormous genetic variability of the virus. The requirement for sequential interactions between the viral envelope and key host receptors/co-receptors may provide new drug targets that could be exploited by small-molecule inhibitors. Recently, Syder *et al.*<sup>[10]</sup> discovered and optimized a series of 1,3,5-triazine compounds that are potent, selective and non-cytotoxic inhibitors of HCV entry. Representative compounds fully suppress both cell-free virus and cell-to-cell spread of HCV *in vitro*. To date, only one oral HCV entry inhibitor with a defined mechanism of action, ITX-5061, has entered clinical testing (phase 2a)<sup>[11]</sup>. ITX-5061 binds directly to SR-B1 and blocks a key post-binding step in the viral entry process. In chronically infected patients we cannot find a single isolate of HCV but rather a population of related yet different viral variants (quasispecies), containing a vast repertoire of preformed variants that allow rapid escape from selective pressures such as neutralizing antibodies or anti-viral drugs. Recently, two well-known molecules have been shown to inhibit HCV entry: the green tea catechin epigallocatechin-3-gallate (EGCG) and the tyrosine kinase inhibitor erlotinib. Erlotinib blocks HCV entry by inhibition of the activity of the epidermal growth factor receptor which is required for formation of CD81-claudin-1 co-receptor associations<sup>[12]</sup>. EGCG inhibits viral attachment to the target cell as well as cell-to-cell transmission between adjacent cells.

#### Role of Niemann-Pick C1-like 1 cholesterol absorption receptor in viral entry

Sainz *et al.*<sup>[13]</sup> have recently discovered a novel surface

receptor involved in HCV entry, the Niemann-Pick C1-like 1 cholesterol absorption receptor (NPC1L1), a 13transmembrane-domain cell surface cholesterol-sensing receptor, expressed on the apical surface of intestinal enterocytes and human hepatocytes, including Huh7 cells, is responsible for cellular cholesterol absorption and whole-body cholesterol homeostasis. NPC1L1 was first identified as a homolog of Niemann-Pick C1 protein<sup>[14]</sup>, the deficiency of which causes Niemann-Pick disease type C1, a genetic disorder characterized by intracellular accumulation of unesterified cholesterol in the endosomal/lysosomal system of neurons that causes neurodegeneration and premature death<sup>[15,16]</sup>. Human *NPC1L1* gene maps to chromosome 7p13, spans 29 kb, encodes a 5 kb mRNA and predominantly produces a protein of 1332 amino acids<sup>[17]</sup>. NPC1L1 locates to the brush border membrane of the enterocyte and the canalicular membrane of the hepatocyte. Biliary cholesterol, which is secreted into bile by hepatocytes, accounts for more than two thirds of the total amount of cholesterol in the gut lumen. Since the cholesterol is water-insoluble, it is delivered to the brush border membranes by bile salt micelles.

These authors have shown that using NPC1L1-specific antibody, HCV infection was reduced in a similar way that CD-81 specific antibodies did. Ezetimibe is a 2 azetidinone-class drug that has been approved by the Food and Drug Administration as a cholesterol-lowering medication<sup>[18]</sup>. Sainz *et al.*<sup>[13]</sup> also shown the role of NPC1L1 receptor on HCV infection *in vivo*, using immunodeficiency mice repopulated with human hepatocytes and treated them *via* oral gavage with ezetimibe. They have demonstrated that ezetimibe treatment delayed the establishment of HCV infection in mice pretreated for 2 wk, confirming the ability of this drug to inhibit HCV infection *in vivo*. However, ezetimibe concentration in those experiments was high (30  $\mu$ mol/L). That means for a 70 kg weight adult to ingest 84 ezetimibe 10 mg tablets per day, when the usual doses for ezetimibe is one 10 mg tablet per day. So far, an ezetimibe based therapy for HCV does not seem suitable. Probably the use of antibodies against NPC1L1 would be a better alternative.

#### Lipid metabolism and HCV infection

HCV infection is tightly associated with alterations in lipid metabolism and lipids have been shown to play important roles during the viral replication cycle<sup>[19,20]</sup>. Indeed, recent studies based on transcriptome and proteomic analyses have demonstrated that expression of host genes involved in the biosynthesis, degradation and transport of intracellular lipids is profoundly altered upon infection. The expression of sterol regulatory element binding proteins, which control transcription of genes required for cholesterol biosynthesis, is stimulated by HCV infection. In agreement with this, the expression of fatty acid synthase (FASN) and other genes related to the synthesis and transport of fatty acids is upregulated in infected cells<sup>[21,22]</sup>. Moreover, the inhibition of FASN

activity blocks HCV RNA replication and production of infectious virus particles<sup>[23]</sup>. Finally, expression of genes regulating geranylgeranylation of cellular proteins important for HCV replication is also upregulated in HCV infected cells<sup>[21]</sup>.

HCV from infected patients (sera) can be precipitated with antibodies against lipoproteins (LP), indicating that HCV circulates associated to LP. Removal of LP by apheresis reduced HCV RNA level by 77%, suggesting that most of the viral particles are tightly associated with lipoproteins<sup>[24]</sup>. Two different studies<sup>[25]</sup> suggest that infectious HCV particles are highly associated with LP. Lipoproteins are easily endocytosed, supporting the hypothesis that HCV can use this association to LP to adhere the cell and subsequently enter into the host cell by endocytosis rather than direct fusion to the membrane<sup>[26]</sup>.

Lipids droplets are necessary for the lipovirion formation. HCV is hypothesized to initiate assembly in close association with lipid droplets by coating lipid droplets with the core protein and bringing together nonstructural (NS) and structural proteins in a NS2-dependent manner<sup>[27-29]</sup>. Following capsid assembly, nascent virions bud into the lumen of the endoplasmic reticulum (ER) where the glycoproteins E1/E2 reside in addition to the very low density lipoprotein (VLDL) secretion machinery. HCV is infectious upon envelopment at the ER, and it is thought that apolipoprotein E (ApoE) is acquired early during assembly because knockdown of ApoE reduces intracellular and extracellular virus; also NS5A interacts with ApoE<sup>[30,31]</sup>. Core proteins disturb microsomal triglyceride transfer protein (MTP) activity in the hepatocyte<sup>[32]</sup> and it has been described that NS5A could be interfered with MTP function. MTP is an essential chaperone for the assembly of VLDL, which transfers triglyceride, phospholipids, and cholesterol from the hepatocytes. Reduced activity of MTP results in decreased secretion of VLDL, leading to lipid accumulation. This fact could explain development of steatosis.

The low-density lipoprotein receptor (LDLR) was proposed as a potential entry factor for HCV<sup>[33]</sup>, however, its implication in virus entry remains unclear. Moreover, by using HCV particles isolated from patients, a correlation has been shown between the accumulation of HCV RNA into primary hepatocytes, expression of LDLr messenger RNA, and LDL entry<sup>[34]</sup>. The potential involvement of the LDLr in HCV entry has also been reported in the HCVcc system<sup>[35]</sup>. Albecka *et al.*<sup>[36]</sup> have shown that HCV particles can interact with the LDLr. However, this interaction does not necessarily lead to a productive infection. Furthermore, those data indicate a role for the LDLr as a lipid-providing receptor, which modulates viral RNA replication.

Quercetin, an abundant flavonoid found in fruits and vegetable, has been implicated in lowering the risk of cardiovascular disease that is often associated with high plasma levels of LDL cholesterol. Quercetin was found to inhibit NS3 activity in a specific dose-dependent manner in an *in vitro* catalysis assay, also inhibiting HCV

RNA replication in the subgenomic HCV RNA replicon system and virus production in the HCV infectious cell culture system<sup>[37]</sup>. Gonzalez *et al.*<sup>[38]</sup> have shown the marked reduction in viral production imparted by heat shock proteins synthesis inhibitor Quercetin. The low toxicity and pharmacokinetics of Quercetin are well known, and it has been approved for other uses in clinical trials. In fact, a phase I study evaluating the safety and tolerability of Quercetin in hepatitis C patients who have contraindications to standard antiviral treatment started last year ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

Administration of the exogenous interferons (IFNs) alpha, beta, and gamma in the setting of treatment for chronic HCV infection and other conditions has been shown to lower LDL cholesterol and raise triglyceride levels in VLDL, concomitant with suppression of lipoprotein lipase<sup>[39,40]</sup>. Li *et al.*<sup>[41]</sup> have shown an association between rs12979860 genotype and host serum lipid levels, suggesting a relationship between endogenous IFN response and lipids. They hypothesize that the IFN-lambda rs12979860 CC responder genotype, which was associated with both increased likelihood of treatment response and higher LDL cholesterol levels in the studied cohort, is associated with lower IFN-lambda activity or lower intrahepatic IFN signaling gene expression. Our results indicate that LDL and total cholesterol levels were higher in patients infected with HCV genotype 1 harbouring the favourable genotype for interleukin 28B gene (Del Campo *et al.*<sup>[29]</sup> unpublished data). These results suggest that observed associations are directly related to HCV-host interactions instead of a direct effect of this locus on lipid metabolism. At least in part, this host factor could select virus infection and promote chronic infection or spontaneous clearance according to viral genotype and lipid metabolism interplay.

### Final remarks

HCV entry is a highly orchestrated process involving several viral and host cell factors, affecting infection, spontaneous viral clearance, persistent infection and widespread, and thereby offering multiple novel targets for antiviral therapy. A recently discovered novel surface receptor involved in HCV entry, NPC1L1, is responsible for cellular cholesterol absorption. This receptor arose as a new therapeutic target for HCV infection, since specific antibodies can block HCV entry. Ezetimibe treatment delayed the establishment of HCV infection in an animal model, emphasizing the relevance of the interaction between the host lipid metabolism and the establishment of a persistent infection, although utilized doses could not be translate to clinical practice. Host and virus genetic variation together with the interaction with hepatocyte receptors were assumed to explain the heterogeneity in HCV outcomes across individuals.

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