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MINIREVIEWS

Roles of lipoprotein receptors in the entry of hepatitis C virus

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Abstract

Infection by hepatitis C virus (HCV), a plus-stranded RNA virus that can cause cirrhosis and hepatocellular carcinoma, is one of the major health problems in the world. HCV infection is considered as a multi-step complex process and correlated with abnormal metabolism of lipoprotein. In addition, virus attacks hepatocytes by the initial attaching viral envelop glycoprotein E1/E2 to receptors of lipoproteins on host cells. With the development of HCV model system, mechanisms of HCV cell entry through lipoprotein uptake and its receptor have been extensively studied in detail. Here we summarize recent knowledge about the role of lipoprotein receptors, scavenger receptor class B type I and low-density lipoprotein receptor in the entry of HCV, providing a foundation of novel targeting therapeutic tools against HCV infection.

Key words: Lipoprotein receptors; CD81; Scavenger receptor class B type I ; Hepatitis C virus entry; Low-density lipoprotein receptor

Core tip: As cirrhosis and hepatocellular carcinoma caused by hepatitis C virus (HCV) is one of the major health problems in the world, the investigation of HCV infection becomes more and more important. HCV entry is the initial step to start infection and is a multiple process involved in abnormal metabolism of lipid. Hence, here we summarize recent knowledge about the role of lipoprotein receptors for better understanding of HCV.

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INTRODUCTION

Hepatitis C virus (HCV) mainly affects liver and causes infectious disease hepatitis C in the world[1]. As a RNA virus, HCV infects about 2%-4% of people all over the world and induces kinds of liver diseases, including about 343000 deaths due to liver cancer from HCV occurred in 2013 up from 198000 in 1990 and an additional 358000 in 2013 occurred due to cirrhosis[2]. Different from hepatitis A virus and hepatitis B virus, there is no available vaccine against HCV until now, and current therapy for HCV infection is based on direct-acting antivirals with or without peginterferon plus ribavirin[3,4]. Hence, knowing the mechanism of HCV infection is becoming more and more important.

HCV AND ITS STRUCTURE

The HCV belongs to the family Flaviviridae and is a kind of the genus hepacivirus. Based on the differences of nucleotide sequence, which is 30%-35% varying over the complete genome, it is classified into seven genotypes[5]. Sixty percent of all cases are caused by subtypes 1a and 1b and both types of HCV are able to be found all around the world. For further study on HCV entry and the elucidation of the mechanisms of HCV infection, HCV-like particles (HCV-LP), HCV pseudotyped particles (HCVpp) and HCV cell culture (HCVcc) system is widely developed recently[6-8]. HCV-LPs, production of baculovirus expression systems, can infect both hepatoma cells and human primary hepatocytes by the mediation of its receptors[9]. However, they are lack of reporter to reflect the earliest stages of infection[10]. The disadvantage of HCV-LPs is made up by HCVpp, which is produced by lentiviral particles incorporating unmodified HCV glycoproteins into the lipid envelope[11,12]. HCVpp mimics the very early stage of cell entry by carrying a marker gene. Only one deficiency of HCVpp system, they cannot be associated with lipoproteins, because it is lack of lipoproteins in the producing cells, 293T kidney cells[10]. Following, HCVcc system is developed to represent the complete replication cycle of virus and to release the production of authentic virus particles that are able to infect *in vitro* and *in vivo*[13,14]. Until now, HCVcc system is the only model system which can completely mimic a natural HCV infection, although its recipient cells are limited to two specific cell lines, LH86 and Huh-7[10]. Unfortunately, there are few suitable small animal models for the research of HCV and only used for certain aspects of HCV infection *in vivo*[15,16].

In a typical HCV particle, a core of genetic material (a positive single-standard RNA), which consists of a single open reading frame of 9600 nucleotide bases long, is surrounded by a protective shell of nonstructural protein (NS2, NS3, NS4A, NS4B, NS5A and NS5B), and further encased in a lipid envelope[10]. There are two kinds of viral envelope glycoproteins, E1 and E2, which are embedded in the lipid envelope. Since non-structural proteins play important roles in viral self-replication, both envelope proteins are necessary and serve as the fusogenic subunit during the process of HCV entry; particularly, E2 acts as the receptor binding protein[17,18]. Based on this, soluble form of recombinant E2 glycoprotein (sE2) was synthesized to study the receptors of HCV in cell entry[19,20].

HCV INFECTION

Infecting a target cell by HCV entails an orchestrated process which can be described into several steps starting from the binding of the viral particles to receptors with co-receptors[21]. Usually, the interaction of glycoproteins (E1 and E2) on the viral surface and specific receptors on the surface of target cell determines the association of a HCV with a target cell. Here, we define the process of viral entry into cells into a three-step process (Figure 1). Initially, HCV recognizes a target cell by binding to the mannose-binding lectins L-SIGN, which is mainly expressed on the endothelium of liver and DC-SIGN, which is expressed on dendritic cells. Both of the cell surface proteins are believed to function as HCV capture receptors[22]. Laterly, the viral glycoproteins interacts with the CD81 tetraspanin[23] and lipoprotein receptors[24-26], transferring the virus from the surface to side gradually. Finally, tight junction proteins may be utilized to help HCV entry by inducing clathrin-mediated endocytosis.

ROLE OF CD81 TERASPANIN IN THE ENTRY OF HCV

During the process of HCV cell entry, CD81 teraspanin, which contains a small extracellular loop, a large extracellular loop (LEL), four transmembrane domains and intracellular N- and C-terminal domains, plays an important role. It was firstly reported that CD81 interacted with a soluble HCV glycoprotein E2 and blockade of CD81 by a specific antibody or silencing of CD81 inhibited the HCV entry and decreased HCV infectivity, demonstrating that CD81 is necessary for the entry of HCV[19,27,28]. In more detailed, the initial step of HCV binding to CD81 is actually the linking between HCV glycoprotein E2 and the LEL of CD81[29], showing LEL served directly in HCV entry. Subsequent research pointed out the relation between CD81 expression on cell surface and membrane lipid composition, that ceramide enrichment of the plasma membrane strongly inhibited the expression of CD81. As lipids organization on the membrane of host cells is essential for HCV entry, internalization of CD81 induced by ceramide inhibited HCV entry[30]. In HepG2 cells and Huh-7, which are derived from hepatoma, CD81 was also demonstrated to affect the susceptibility to HCV infection and the efficiency of HCV entry[31-33]. In addition, the dynamic

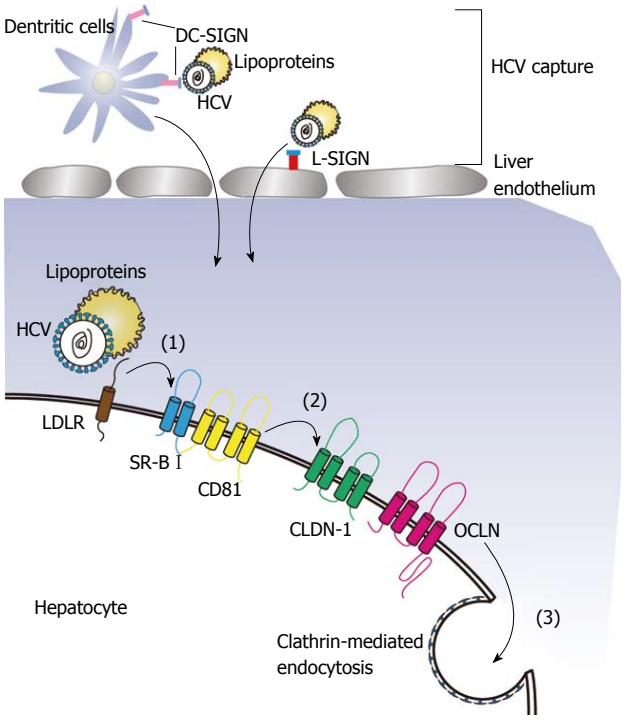

Figure 1 Process of hepatitis C virus cell entry. After being captured by DC-SIGN and L-SIGN, virions with apolipoprotein may first attach a host cell by interacting with LDLR on the cell surface (1), following by binding to CD81 and SR-B Ⅰ (2), and finally by a later utilization of the tight junction protein CLDN1 and OCLN (3). HCV: Hepatitis C virus; SR-B Ⅰ: Scavenger receptor class B type Ⅰ; LDLR: Low-density lipoprotein receptor; CLDN-1: Claudin-1; OCLN: Occluding.

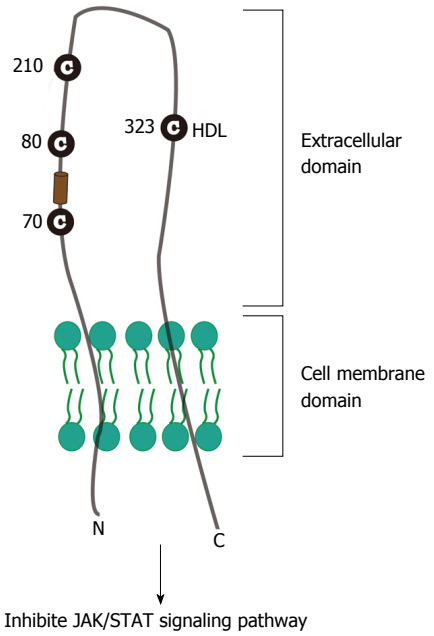

Figure 2 Model of scavenger receptor class B type Ⅰ topology and its relevance for hepatitis C virus entry. The SR-BI regions comprise cytoplasmic C-terminal and N-terminal domains separated by a large extracellular domain. Cholesterol uptake and HCV entry is mainly mediated by extracellular domain. Particularly, C323 is critical for SR-BI-mediated cholesterol ester uptake. Amino acids 70-87 and the single residue E210 of SR-BI are required for E2 recognition in HCV entry. SR-B Ⅰ: Scavenger receptor class B type Ⅰ; HCV: Hepatitis C virus; HDL: High-density lipoprotein; JAK/STAT: Janus kinase/signal transducer and activator of transcription.

of CD81, which is dependent on the hepatocytes polarization, could regulate HCV infection[34] and the trafficking of CD81 on the host cell membrane promoted claudin-1-dependent HCV particle internalization[35]. Recently, it was demonstrated that the expression of CD81 also modulated HCV RNA replication[36], suggesting that the HCV life-cycle also requires CD81.

Recent study pointed out that multiple RTKs could mediate HCV entry by regulating CD81-claudin-1 and viral glycoprotein-dependent membrane fusion[37]. Liu *et al*[38] also found that HCV transiently activates the phosphatidylinositol-3-kinase/AKT pathway to facilitate its entry. These findings may contribute to a new approach to prevention and treatment of HCV infection.

ROLE OF LIPOPROTEIN RECEPTORS IN THE ENTRY OF HCV

The metabolism of apolipoproteins, lipids and lipoproteins is mainly regulated by the liver and HCV attacks liver, leading to abnormal serum lipoproteins and accumulation of lipids in hepatic cells in a chronic mode[39-41]. In recent years, the relationship between cholesterol metabolism and fatty acid biosynthetic pathways in target cells and HCV infection has gained much attention. As a result, the role of lipoprotein receptor in the HCV entry is extensively investigated in detail. Hence, we will focus on roles of the two lipoprotein receptors, scavenger receptor class B type Ⅰ (SR-B Ⅰ) and low-density lipoprotein receptor (LDLR) in this review.

SR-B Ⅰ

SR-B Ⅰ, as a 509 amino acid glycoprotein, is an integral membrane receptor with cytoplasmic C-terminal and N-terminal domains separated by a large extracellular domain (Figure 2); and is found in numerous cell types and tissues, including the liver and adrenal. There are evidences that SR-B Ⅰ selectively mediates uptake of high-density lipoprotein (HDL) cholesterol ester (CE) into transfected Chinese hamster ovary cells[42] and C323 of SR-B Ⅰ is critical for SR-B Ⅰ-mediated cholesterol ester uptake[43]. Previous study also proves that the human homologue of SR-B Ⅰ, CD36 and LIMPII Analogous-1 (hSR-B Ⅰ/CLA-1), serves as a receptor of HDL and regulates cholesterol efflux to HDL during the process of reverse cholesterol transport[44-47].

Recent reports indicate that HDL promoted HCV entry and this enhancement was mediated by the formation of SR-B Ⅰ, HDL and HCV envelope glycoproteins complex[20,48,49]. Many groups demonstrated that the glycoprotein E2 could bind SR-B Ⅰ in hepatoma cells: Scarselli *et al*[20] demonstrated that extracellular domain of SR-B Ⅰ interacts with E2 hypervariable region 1 (HVR1)[20,26]; Catanese *et al*[50] found out that amino acids 70-87 and the single residue E210 of SR-B Ⅰ are required for E2 recognition, raising a possibility for new therapeutic strategies targeting virus/SR-B Ⅰ recognition.

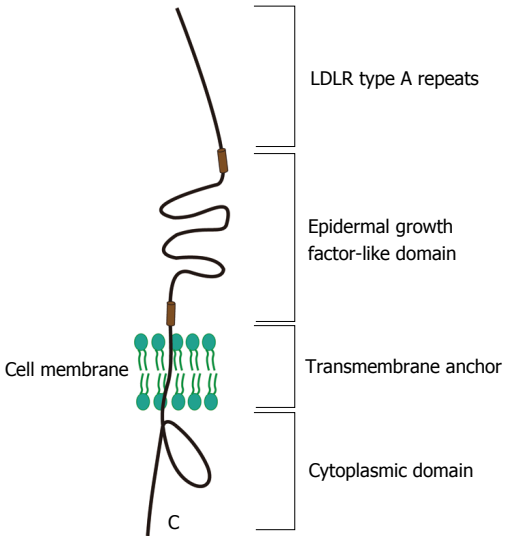

Figure 3 Structure of low-density lipoprotein receptor and its relevance for hepatitis C virus entry. LDLR is structurally composed by four motifs: LDLR type A repeats, which is the main binding site for ligand; an epidermal growth factor-like domain, which is response to the change of pH to release ligand; a transmembrane anchor and a cytoplasmic domain, which mediates clustering of the receptors into the clathrin-coated pit. LDLR: Low-density lipoprotein receptor.

Based on the detailed internship between virus and SR-B Ⅰ, Murao *et al*[25] point out that interferon alpha decreases the efficiency of HCV infection by down regulating the binding of SR-B Ⅰ with both synthesized E2 region-Ⅰ (4931) and E2 region-Ⅱ (4938) peptides in HepG2 cells. Vercauteren *et al*[51] recently found a new anti-SR-B Ⅰ antibody, small molecule inhibitors monoclonal antibody1671 (mAb1671), significantly inhibited infection of hepatoma cells with wild-type HCV by inhibiting the function of SR-B Ⅰ, suggesting that mAb1671 could be used as a therapeutic antibody.

SR-B Ⅰ not only acts as a binding receptor of HCV, but also plays a critical role in the post-binding steps. Catanese *et al*[50] and Zeisel *et al*[52] showed that the susceptibility of human hepatoma cells to HCVcc infection is markedly reduced by silencing of SR-B Ⅰ with specific siRNA, SR-B Ⅰ specific antibody or mutation of SR-B Ⅰ and the effect is independent of lipoprotein, pointing out the role of SR-B Ⅰ in the post-binding process.

HCV particles associated with plasma lipoproteins like HDL can be found in the viral particles isolated from patients and the abnormal metabolism of lipid influences the HCV infection, suggesting that HCV entry might also potentially involve the interactions with SR-B Ⅰ ligands, HDL. Although HCVpp is not able to interact with HDL apolipoprotein, the increase of HDL still markedly induces the enhancement of HCVpp entry, while inhibition of the transfer of HDL CE reduces the entry of HCVpp into cells[49,53]. However, the ability of HDL to facilitate HCV entry is largely in a SR-B Ⅰ -dependent manner since silencing of this receptor cancelled the effect of HDL on enhancement of viral entry[49].

Another goal of recent researches was to examine the signaling pathways involved in the HCV infection in more detail. After binding of glycoprotein E2 to SR-B Ⅰ, multiple signaling pathways will be inactivated to facility HCV entry in host cells. There is a report points out that HCV selectively decreased the abundance of signal transducer and activator of transcription 1 (STAT1) and reduced the phosphorylation of STAT1 in the nucleus by binding its core protein to STAT1 in a proteasome-dependent manner to defense the immunity induced by JAK/STAT pathway[54]. In turn, the treatment with interferon alpha was proved to phosphorylate STAT1 to protect the host cells from infection of HCV[25]. STAT3 activation in human hepatocytes was also confirmed to resist an attack from HCV infection *in vitro*[55]. Clinically, treatment with interferon alpha and ribavirin is one of the therapies for chronic HCV infection. Type 1 interferon is a production from host cells infected with virus and constitute the primary defense mechanism against viral infection and replication[56]. Secreted interferon acts through an autocrine and paracrine loop that requires intact interferon receptor and JAK/STAT pathways involving STAT family members[57].

In summary, all of these evidences point out the critical role of SR-B Ⅰ in enhancing HCV entry into hepatic cells and the complicated process requires the complex between lipoproteins, SR-B Ⅰ, and HCV envelope glycoproteins. The *SR-B Ⅰ* gene is able to transcript into two mRNA splice variants, SR-B Ⅰ and SR-B Ⅱ and the two variants are different from their C-termini. Although there is evidence that HCV soluble envelope glycoprotein E2 is able to interact with not only human SR-B Ⅰ but also SR-B Ⅱ[58], the role of SR-B Ⅱ in the HCV entry is rarely reported.

In the family of scavenger receptors, there is another member named scavenger receptor class A (SR-A), which is mainly expressed in macrophage. It is composed of a cytosol domain, a transmembrane domain, a spacer domain, an alpha-helical coiled-coil domain, a collagen-like domain and a cysteine-rich domain and has two different types, SR-AI and SR-AII[59]. Different from the SR-B, the main function of SR-A in innate immunity is defense of bacteria. Recently, it was reported that SR-AI could bind to the non-structural protein NS3 of HCV in dendritic cells, pointing out that SR-A may serve as endocytic innate receptors in NS3 recognition[60].

LDLR

LDLR is another potential lipoprotein receptor involved in HCV infection of hepatocytes. LDLR (Figure 3), an 893 amino acids transmembrane protein, is a cell surface receptor that mediates uptake of cholesterol-rich low-density lipoprotein (LDL)[61,62]. When the main ligand cholesterol-LDL binds to the receptor, it is transferred into hepatic cells by clathrin-mediated endocytosis and then the receptor will release the bound LDL particle because of the conformational change induced by change in pH. Accumulation of serum LDL directly leads to the development of atherosclerosis.

Since Agnello *et al*[63] firstly suggested the role of LDL-R in HCV entry in 1999, most studies focus on its role as a receptor of HCV or facilitating initial attachment to cell surface[10]. André *et al*[64] reported that lipo-viro-particles isolated from patients with hepatoma infect hepatic cells in an LDLR-dependent manner, indicating the important role of LDLR in HCV infection. In coincidence with this report, LDLR is confirmed to take part in an early stage in infection of normal human hepatocytes by serum-derived HCV virions *in vitro*[65]. A human study that LDLR expression of 68 patients with HCV chronic infection was significantly associated with HCV-viral load, supplies the evidence that the LDLR may be one of the receptors implicated in HCV replication[66].

While HDL facilities the entry of HCV into hepatic cells, LDL could significantly inhibit the cell entry of serum HCV and HCVpp *via* LDLR. Some studies also reported that ApoE-containing very LDL, as a ligands of LDLR, mediates the HCV entry *in vitro*. Recently, Ficolin-2, as a lectin-complement pathway activator, inhibited the chronic HCV infection by inhibition the function of LDLR and SR-B Ⅰ and this effect was blocked by ApoE3-mediated immune escape[67]. It was confirmed by a recent report that ApoE3 and ApoE4 rescue the production of infectious virus and it requires both the LDLR and SR-B Ⅰ [68]. By contrast, Prentoe *et al*[26] found in the process of HCV entry, the function of LDLR is in an ApoE-independent but E2 HVR1-dependent manner. Although there are lots of evidences to prove that LDLR, the same as SR-B Ⅰ and CD81, plays a critical role in the initial step of HCV entry, one of studies suggested that LDLR is not necessary for HCV entry and implied the physiological function of LDLR in HCV replication[69]. Recently, it was demonstrated that HCV upregulates the expression of LDLR *via* SREBPs and PCSK9 at both transcriptional and posttranslational level to increase the uptake of lipid and to promote viral proliferation[70]. Until now, there is no doubt that LDLR is able to mediate the HCV infection. However, the detailed mechanism how it really works during this complex process needs to be further investigated.

ROLES OF TIGHT JUNCTION PROTEINS IN THE LATER PHASE OF HCV ENTRY

By using screening cDNA library, two kinds of tight junction proteins, claudin-1 (CLDN-1) and occludin (OCLN), were identified as factors that are able to affect the HCV entry in the later phase[71,72]. Either CLDN-1 or OCLN contains four transmembrane domains and two extracellular loops with the N-terminus and C-terminus in the cytoplasm. Interestingly, there is no evidence to confirm that there is direct interaction between CLDN-1 or OCLN and HCV particles. However, it was proved that CLDN-1 directly interacts to CD81 and the association increases the virus entry in the later phase[73]. Laterly, Krieger *et al*[74] produced CLDN-1 specific antibody and found it inhibited HCV infection by reducing the binding of E2 with host cell surface and disrupting the formation of CD-81-CLDN-1 complex. OCLN is also able to interact directly with E2, and silence of CLDN-1 and OCLN by specific siRNA reduced both HCVpp and HCVcc cell entry[75].

OTHER FACTORS ON CELL SURFACE INVOLVED IN HCV ENTRY

Besides the receptors we talked above, there are some other factors on host cell surface, which are believed to be functional in HCV entry. Lupberger *et al*[37] pointed out the important role of epidermal growth factor receptor (EGFR) and ephrin receptor A2 (EphA2) as cofactors in HCV entry. EGF accelerated HCV entry by activating signaling pathways and inhibition of EGFR or EphA2 activity reduced CD81-CLDN1 association. Following, Diao *et al*[76] confirmed that EGFR internalization and activation are critical for HCV entry and firstly identified a hitherto-unknown association between CD81 and EGFR by using HCVcc system. Based on these theories, Meyer *et al*[77] recently supposed a model that interferon-α inducible protein 6 inhibits HCV entry by impairing EGFR mediated CD81/CLDN1 interactions. Niemann-Pick C1-like 1 (NPC1L1), as a cholesterol uptake receptor was firstly identified as an HCV entry factor by Sainz *et al*[78] and they also proved clinically available FDA-approved NPC1L1 antagonist ezetimibe potently blocks HCV uptake *in vitro via* a virion cholesterol-dependent step, discovering a new antiviral target and potential therapeutic agent. Furthermore, transferrin receptor 1 has also been reported as a receptor for HCV entry[79]. However, the roles of these new factors in HCV entry remain to be determined in detailed.

CONCLUSION

The process of HCV entry is a multi-step process and the major steps have already been described as the combination of HCV glycoprotein and targeting cell-surface molecules, such as CD81 and lipoprotein receptor SR-B Ⅰ and LDLR. With the development of HCV model system, the role of lipoprotein and its receptor in HCV infection is more and more detailed understood. However, since all the model system has their own limitations, the results obtained by using system in vitro do not completely reflect the *in vivo* situation. Further studies are required, especially by using engineering new animal models, for HCV infection, and a detailed understanding of the mechanism of HCV entry will give a sufficient groundwork for the development of new therapeutic drugs and tools.

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