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REVIEW

Cellular factors involved in the hepatitis C virus life cycle

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Abstract

The hepatitis C virus (HCV), an obligatory intracellular pathogen, highly depends on its host cells to propagate successfully. The HCV life cycle can be simply divided into several stages including viral entry, protein translation, RNA replication, viral assembly and release. Hundreds of cellular factors involved in the HCV life cycle have been identified over more than thirty years of research. Characterization of these cellular factors has provided extensive insight into HCV replication strategies. Some of these cellular factors are targets for anti-HCV therapies. In this review, we summarize the well-characterized and recently identified cellular factors functioning at each stage of the HCV life cycle.

Key Words: Hepatitis C virus; Cellular factor; Viral entry; Translation; Replication; Assembly; Release

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Core Tip: The hepatitis C virus (HCV) depends on its host cells to propagate successfully. Hundreds of cellular factors involved in the HCV life cycle have been identified. Some of these cellular factors are potential targets for anti-HCV therapies (*e.g.*, scavenger receptor class B type 1, epidermal growth factor receptor, Niemann–Pick C1-like 1, microRNA-122, cyclophilin A). A successful vaccine for HCV is still a challenge in the near future. Investigating the cellular factors involved in viral entry should help vaccine development. HCV is also a unique model to study the interactions between viral infection and cellular lipid metabolisms.

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INTRODUCTION

Around 50%–80% of patients infected with the hepatitis C virus (HCV) will develop chronic infection. Approximately 71 million individuals are chronically infected by the HCV worldwide according to an estimation by the World Health Organization (https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/).

Chronic hepatitis C (CHC) patients are at high risk of developing liver cirrhosis and even hepatocellular carcinoma. Although CHC can now be cured using various direct-acting antivirals, the majority of CHC patients remain undiagnosed and, thus, untreated. Furthermore, a successful antiviral treatment does not prevent HCV reinfection. Therefore, HCV eradication remains a challenge and will probably require an effective vaccine[1] (for a review see References[2,3]).

HCV belongs to the family *Flaviviridae* and genus *Hepacivirus*. Its genome is a single-stranded RNA with positive polarity that is packaged by viral core protein and enveloped by a lipid membrane containing two viral glycoproteins (*i.e.*, E1 and E2) to form the virion. HCV genomic RNA sequences are highly heterogeneous among different isolates. At present, HCV is classified into at least six major genotypes (1 to 6). HCV heterogeneity hinders the development of an effective vaccine to protect against infection from all HCV genotypes. Despite the sequence variations, all currently recognized HCV genotypes are pathogenic, hepatotropic and preserve the similarity of the life cycle in cells (for a review see References[4,5]).

The HCV life cycle begins with the binding of a virion to its specific entry factors (or receptors) on hepatocytes. After binding, the virion is internalized into the cytoplasm and its genomic RNA is released. Then, the HCV genomic RNA is used for both polyprotein translation and viral replication. HCV replication takes place within the membranous web (MW) in the endoplasmic reticulum (ER). At last, HCV uses the biosynthetic pathway of very-low-density lipoprotein (VLDL) to assemble and release the viral particles from cells (for a review see Reference[6]).

HCV relies significantly on its host cells to establish a successful infection due to the fact of its limited genetic content. Hundreds of cellular factors have been identified as being involved in the HCV life cycle over more than thirty years of research. In this review article, due to the limited space, we can only summarize the well-characterized and recently identified cellular factors involved in the HCV life cycle but not including immune responses against viral infections (for a review see Reference[7]).

HCV PARTICLES

It has been demonstrated that purified HCV particles are spherical and heterogeneous in size (40–100 nm in diameter) with no obvious symmetry under cryo-EM[8]. The density of HCV particles in the plasma of CHC patients also varied (from 1.03 to 1.25 g/mL). Low-density HCV particles with 81–85 nm diameters are highly infectious[8,9]. The HCV particles with low density are associated with apolipoproteins (Apo such as Apo-E, Apo-AI, Apo-CI and Apo-B), phospholipids (such as phosphatidylcholine and sphingomyelin) and cholesterol (free and esterified), while they have almost no phosphatidylserine (PS) and very little amounts of phosphatidylethanolamine[8,10-12]. HCV particles derived from cultured cells show characteristics similar to those from CHC patients[9,10,13]. Thus, these circulating HCV particles are referred to as "lipo-viro particles" (LVPs)[14] and have very low buoyant densities due to the fact of their interactions with lipoproteins in the blood[15] (Figure 1) (for a review see Reference[16]).

Modifications of LVPs could be mediated by lipoprotein lipases (LPLs)[17,18]. LPL was shown to shift the HCV particles to higher densities with diminished HCV infectivity[19,20]. Indeed, LPL lipolytic activity in clinical samples has been reported to be inversely correlated with HCV viremia[21].

More than 40 cellular proteins were found in the HCV particles recently using proteomics analyses, including heat shock cognate protein 70 (HSC70) and nucleoporin 98 (Nup98); both proteins play a role in virus assembly/release[22,23].

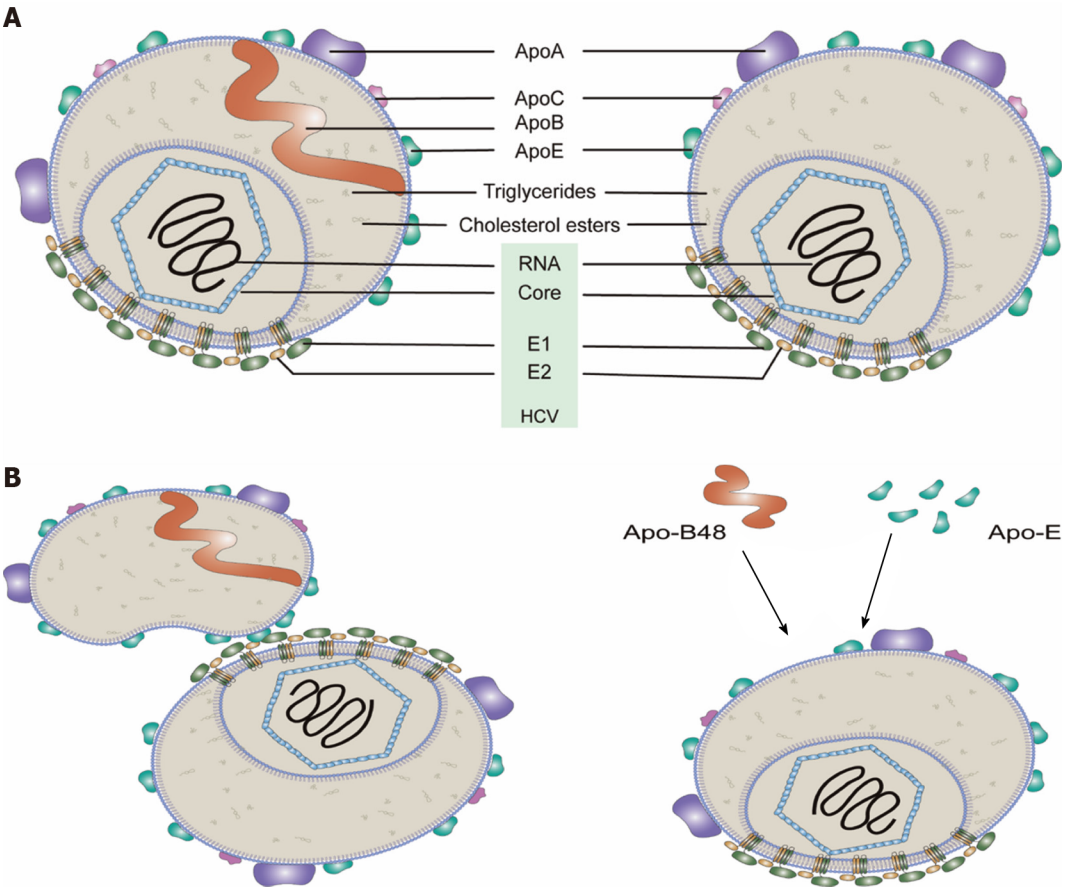

Figure 1 Model of hepatitis C virus particles (lipo-viral particles) secreted from cells. A: Most of the lipo-viral particles (LPV)'s membrane is a lipid monolayer. A bilayer-containing region is where the viral envelope proteins (*i.e.*, E1 and E2) are inserted. Viral envelope proteins may also exist in the phospholipid monolayer membrane. Though the precise structure has not yet been determined, LVPs are believed to have multiple copies of Apo-E and less Apo-A1 molecules but only one Apo-B100 molecule (left). Some LPVs may not have Apo-B (right). Within the phospholipid monolayer, there are the core proteins wrapping the viral RNA genome and neutral lipids (*e.g.*, cholesterol esters and triglycerides); B: Serum lipoproteins are possibly associated with hepatitis C virus particles in different ways. HCV: Hepatitis C virus.

Association of HCV particles with host lipoproteins has advantages for the virus: (1) Lipoproteins likely mask viral epitopes of viral E1 and E2 proteins thus helping the virus escape from the humoral immune response; and (2) Lipoproteins contribute to the hepatotropism of HCV, *e.g.*, HCV attachment to hepatocytes involving Apo-E (and/or Apo-B) binding with the cellular factors [*e.g.*, low-density lipoprotein receptor (LDLR), highly sulfated heparan sulfate proteoglycans (HSPGs) and scavenger receptor class B type 1 (SR-B1)] for viral entry[24].

VIRAL ENTRY

HCV can infect hepatocytes and other cells (*e.g.*, lymphocytes). In general, HCV infects hepatocytes through two distinct routes: Cell-free virus entry and cell-to-cell transmission. Viral entry requires interactions between the components of LPVs (particularly Apo-E and viral envelope proteins) and those of cells (particularly entry factors). Alternatively, HCV may infect cells through exosomes (for a review see Reference[25]).

Cell-free virus entry into hepatocytes

HCV transmission is through the parenteral route, and it needs to reach the liver by crossing the endothelium. Before attachment to the hepatocytes, HCV particles may be captured by DC-SIGN on dendritic cells or L-SIGN on endothelium[26,27] (Figure 2).

Cellular factors responsible for HCV entry into hepatocytes are divided into three groups based on their functions[25,28]: Attachment factors, entry factors (or receptors) and entry cofactors (or facilitators). Attachment factors help dock the virus on the cell's surface, mostly through non-specific interactions. Entry factors mediate specific

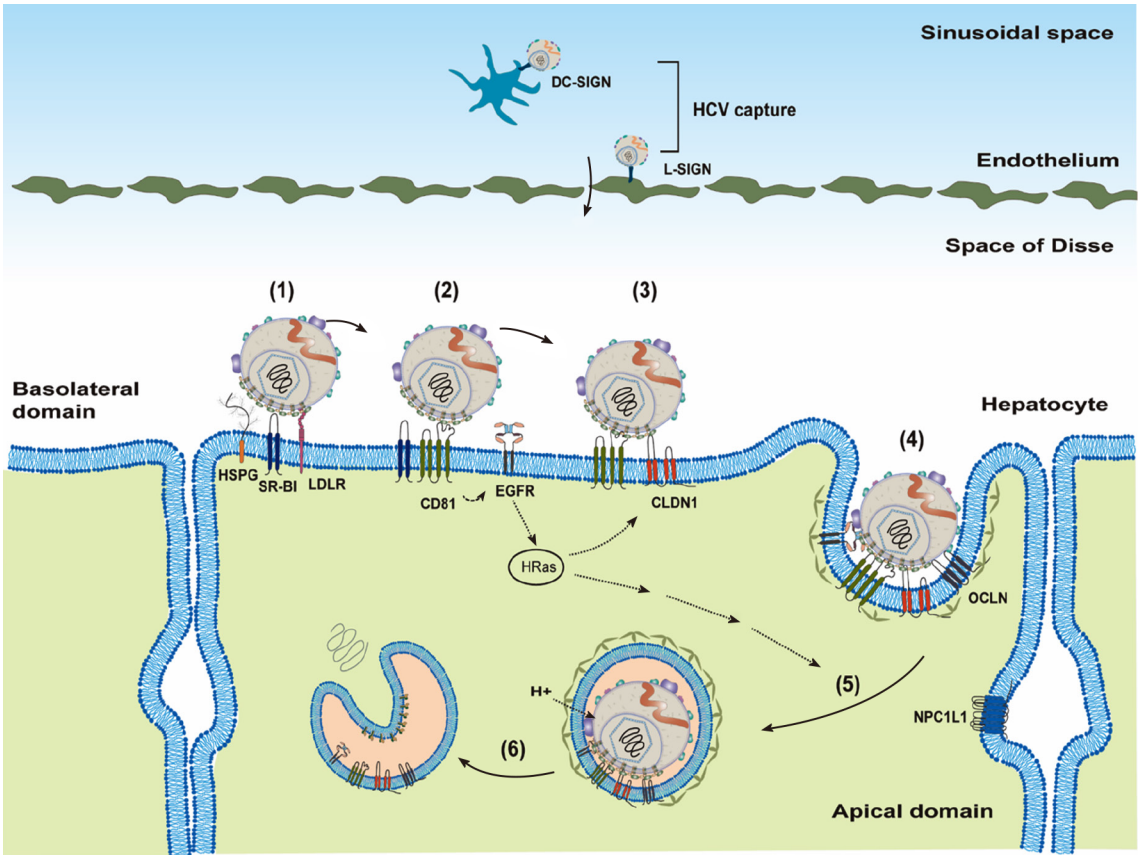

Figure 2 Model of cell-free virus entry into hepatocytes. Hepatitis C virus (HCV) lipo-viral particles (LPVs) may be captured by DC-SIGN on the dendritic cells or L-SIGN on the endothelium in the sinusoidal space. After transfer to Space of Disse, HCV LPVs could attach to the hepatocytes through interacting with highly sulfated heparan sulfate proteoglycans, low-density lipoprotein receptor and scavenger receptor class B type 1 (1). This attachment allows the engagement of LPVs to cluster of differentiation 81 (CD81) and then induces the epidermal growth factor receptor receptor signaling (2). Lateral diffusion of the CD81–HCV complexes results in the association of CD81–HCV with Claudin-1 (3) and then OCLIN (4). Formation of the HCV–CD81–CLDN1–OCLIN complex allows viral particles internalized through clathrin-dependent endocytosis (5). Endosomal acidification induces the fusion of viral particles possibly through E1 and leads to the release of the viral genomic RNA into cytosol (6). HSPGs: Heparan sulfate proteoglycans; HCV: Hepatitis C virus; EGFR: Epidermal growth factor receptor; LDLR: Low-density lipoprotein receptor.

interactions with viral glycoproteins. Entry cofactors, although not interacting directly with the virus, play an important role in supporting viral entry.

To infect a new hepatocyte, the HCV needs to interact with the attachment factors on the basolateral side of hepatocytes first (Figure 2). The well-known attachment factors include HSPGs, (particularly syndecans: SDC-1 and SDC-2), LDLR and SR-B1 [29-32]. Attachment of HCV LPVs to host cells is mediated mainly through the virus-associated lipoprotein components (particularly Apo-E[33]) and viral glycoproteins (E1 and E2, particularly E2)[32,34,35]. In addition to the binding of Apo-E with attachment factors, Apo-B100 could also interact with LDLR[36] and Apo-AI with SR-B1[37]. Recently, the redundant functions of Apo-C1 and Apo-E in the HCV infection have been demonstrated[38]. Attachment to SR-B1 may bring HCV particles to entry factor cluster of differentiation 81 (CD81)[39]. SR-B1, as both an entry factor and an attachment factor, has been shown to bind viral envelope proteins[29,40]. Interaction of HCV with CD81 activates epidermal growth factor receptor (EGFR) signaling and also facilitates CD81 diffusion and formation of the HCV–CD81–CLDN1 complex[39, 41-43]. The HCV–CD81–CLDN1 complex then interacts with OCLN, which is believed to mediate the clathrin-dependent internalization through interacting with GTPase dynamin[44-46]. SR-B1, CD81, CLDN1 and OCLN are four well-characterized entry factors for HCV entry[28]. In addition, LRL-R could interact with both HCV and E2 proteins and, thus, function as an entry factor[47].

HCV particles are then internalized, mature in the acidic endosomes that promote low pH-dependent HCV fusion and, ultimately, release HCV genomic RNAs (uncoating) into cytosol[48-50] (Figure 2). Low endosomal pH and interactions of viral glycoproteins with CD81 are thought to induce conformational rearrangements of viral glycoproteins for HCV fusion[51], which is controlled by E1 protein[52]. Recently, cell death-inducing DFFA-like effector B (CIDEB) protein was identified as an entry

cofactor to act at a late membrane fusion event[53].

Both HCV and coronavirus [*e.g.*, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)][54] are positive-strand RNA viruses. These two viruses enter their target cells through receptor-mediated endocytosis and release their genomic RNAs for translation in the cytosol. However, unlike HCV, coronavirus fusion for viral entry is unusual in that it is often biphasic and can occur at or near the cell's surface or in late endosomes[55].

In addition to HSPGs, LDLR, and SR-B1, interferon receptor IFNAR2 was found as a novel attachment factor to facilitate HCV entry through interacting with Apo-E[56]. VLDL receptor (VLDLR), similar to LDLR, could also serve as an attachment factor for HCV entry[57]. Niemann–Pick C1-like 1 (NPC1L1) contributes to HCV entry possibly through its role as a cholesterol receptor, thus functioning as an HCV entry cofactor [58]. Similarly, PS receptor (TIM-1/human hepatitis A virus cellular receptor 1/CD365) has also been identified as an attachment factor through binding with PS on HCV LPVs[59,60]. It should be noticed that only tiny amounts of PS were detected in the HCV particles[12]. On the other hand, LPLs, hepatic triglyceride lipase and long-chain fatty acyl-coenzyme A can inhibit HCV attachment by targeting virus-associated lipoproteins[17,18,20,61].

In addition to CLDN1, other CLDNs (*e.g.*, CLDN6, CLDN9 and CLDN12) have also been reported as HCV entry factors for some genotypes[62-64]. Recently, CD63 (binding directly with HCV) and CD36 (interacting directly with HCV E1 protein) were demonstrated to be entry factors[65,66]. Under hypoxic conditions, VLDLR could serve as an entry factor independent of canonical CD81-mediated HCV entry[67].

Most cellular factors, not directly interacting with the virus, involved in viral entry are served as the function of entry cofactors[25]. Some entry cofactors were identified to interact with SR-B1 [*e.g.*, PDZK1 and UDP-glucose: Glycoprotein glucosyltransferase 1 (UGGT1)]. The scaffold protein PDZK1 may be involved in linking SR-B1 to the actin cytoskeleton and the endocytic network[68], while UGGT1, a key component of the calnexin cycle involved in protein glycosylation, may stabilize SR-B1[69].

In addition to EGFR signaling, the association of CD81–CLDN1 is also regulated by protein kinase A (PKA)[70], ephrin receptor A2[71] and phosphatidylinositol 4-kinase type III-alpha/beta[72]. These are also entry cofactors supporting viral entry. Several other entry cofactors were identified as CD81-associated factors including HRas[39], integrin 1 (ITGB1)[39], Ras-related protein Rap2B[39], calpain-5[73], ubiquitin ligase Casitas B-lineage lymphoma proto-oncogene B[73] and serum response factor binding protein 1[74]. The membrane lipid composition has been shown to affect CD81 expression on the cell's surface and, in turn, modulate HCV entry[75]. Indeed, depleting cholesterol from the plasma membrane has been shown to decrease viral entry owing to reduced CD81 on the cell's surface[76]. In agreement with these findings, lipid-free Apo-E was demonstrated to induce adenosine triphosphate-binding cassette subfamily G member 1 protein-dependent cholesterol efflux and inhibit HCV replication[77].

Several other entry cofactors affecting CLDN1 and/or OCLN localization are also important in the HCV entry. E-cadherin, tumor-associated calcium signal transducer 2 (TACSTD2) and possibly Rab13 could regulate the localization of CLDN1 and OCLN [78-80]. Cell surface localization of CLDN1 is also regulated by vesicular transport proteins (such as Sec24C)[81]. Serotonin 2A receptor (5-HT2AR) is shown to control CLDN1 localization through PKA-mediated phosphorylation[82].

Several cellular factors involved in the process of HCV internalization have been identified: the expression level of SR-B1[83,84], EGFR–MKNK1 signaling[85,86], Abl tyrosine kinase[87], signaling pathways of Rac/Rho/CDC42/mitogen-activated protein kinase[41], actin[50], transferrin receptor 1[88], adaptor proteins (AP)-2-associated protein kinase 1[89] and cyclin G-associated kinase[89].

Pim kinase[90], Ankyrin repeat domain 1[91] and solute carrier family 3 member 2 [92] proteins are required for HCV entry, though their exact roles are not yet defined. In addition to the clathrin-dependent internalization pathway, HCV could also use clathrin-independent mechanisms to enter different cells[93].

Viral cell-to-cell transmission

In addition to cell-free virus entry into hepatocytes, HCV particles can also transmit directly from an infected hepatocyte to an adjacent hepatocyte[94-96]. A recent study demonstrated that the HCV core, *E1*, *E2* and *P7* genes were essential for not only cell-free viral transmission but also cell-to-cell transmission[97]. Several cellular factors were reported to contribute to HCV cell-to-cell transmission, including CD81[98,99], SR-B1[95], CLDN1[98], OCLN[98], LDLR[98], SDC-1[98], SDC-2[98], TIM-1[98], Apo-E in mature HCV particles[33,98,100], AP-1B and AP-4[101]. However, SR-B1-

independent[102] or CD81-independent[103] HCV cell-to-cell transmission has also been reported. More studies are needed to clarify this issue.

Viral transmission through exosomes

Exosomes, small vesicles normally used for intercellular communication, have been reported containing HCV RNA[104-107]. HCV transmission through exosomes should be independent of any entry factor, and it is resistant to antibody neutralization. However, further investigation is required to understand the mechanisms of transmitting HCV genomic RNA through exosomes[108].

Infection of HCV into other cells

B7.2 (CD86)[109] enabling lymph-tropic HCV to infect memory B cells and CD5[110] important for HCV entry into human T lymphocytes were identified. HCV enters macrophages mainly through phagocytosis[111].

VIRAL PROTEIN TRANSLATION

After the fusion between the viral envelope and the endosomal membrane, HCV positive-strand RNA will be released into the cytosol (Figure 2). Translation of HCV genomic RNA is modulated by the viral RNA structure, cellular translational machinery [*e.g.*, 40S, translation initiation factors (eIFs)] and several cellular regulatory factors [*e.g.*, microRNA-122 (miR122) and internal ribosome entry site (IRES) trans-acting factors (ITAFs)] (for a review see Reference[112]).

The most important structures of the HCV genomic RNA for translational regulation reside in the IRES of the 5'-untranslated region (5'UTR), a short segment of the core gene sequence, the cis-acting replication element (CRE) in the NS5B coding region[113] and the entire 3'UTR[114] (Figure 3). Many long-range RNA–RNA interactions among different regions of the HCV genomic RNA are involved in translational regulation[115]. The HCV IRES could bind to the ribosomal 40S subunit directly[116-118]. Interaction between the viral IRES and cellular 18S rRNA consisting of a three-nucleotide base pairing of these two molecules is crucial for HCV translation [119].

When eIF2–Met–tRNAi Met is available, canonical eIFs, including eIF3, eIF2, eIF1A, eIF5 and eIF5B, can initiate HCV translation[120]. On the other hand, when eIF2–Met–tRNAi Met is limited, eIF2A[121], eIF2D[122], eIF5B[123], a combination of eIF2A and eIF5B[124], or MCT-1 and a DENR protein complex[125] could substitute for eIF2 to initiate the translation (for a review see Reference[112]). A single RNA loop in domain II of the HCV IRES controls the translation from initiation to elongation [126].

The most important cellular factor involved in HCV translation is miR122. The liver-specific miR122 is crucial for HCV production (for a review see Reference[127]). miR122 can bind to two adjacent recognition sites on the HCV 5' UTR with the help of human Argonaute protein 2 (hAgo2)[128-130]. The hAgo2/miR122 complex could alter the HCV 5'UTR structure and promote the IRES formation to enhance viral translation[131].

Several cellular proteins could bind to the HCV 5'UTR directly as ITAFs and enhance the viral protein translation such as La[132], heterogeneous nuclear RNA-interacting protein Q (hnRNP Q; NSAP1)[133], hnRNP L[134], hnRNP D[135], IGF2BP1 (insulin-like growth factor 2 mRNA binding protein 1; IMP-1)[136], poly(C)-binding protein 2 (PCBP2)[137], the LSm1-7 complex[138] and polypyrimidine tract binding protein (PTB)[139]. On the other hand, RNA binding protein 24[140] and Gemin5 would possibly suppress HCV translation[141].

Some proteins do not bind to HCV RNA directly but act through protein–protein interactions to help HCV translation, such as HuR (ELAVL1)[142], and the proteasome subunits[143].

Several other cellular proteins, identified as positive regulators of HCV translation through different mechanisms include MAP kinase interacting serine/threonine kinase 1 (MKNK1), phosphatidylinositol 4-kinase catalytical subunit beta (PI4K-beta) [144], ubiquitin-specific protease 15[145], NSAP1[146], RNA helicase DDX6 (RCK, p54) [147] and heat shock protein 70[148].

In addition to miRNAs and proteins, long non-coding RNA (lncRNA), such as HULC, could enhance HCV translation[149]. Moreover, the PI3K–Akt signal pathway could also upregulate HCV translation through the activation of SREBPs[150].

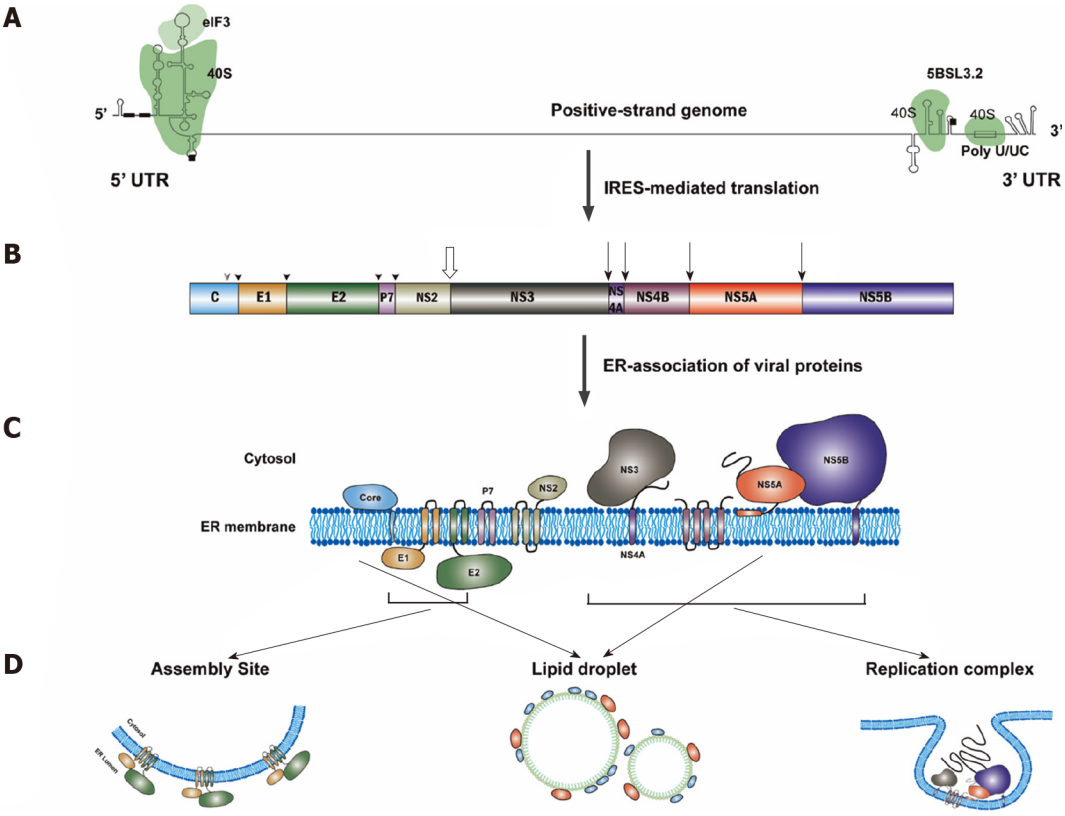

Figure 3 Hepatitis C virus protein translation. A: Translation of hepatitis C virus (HCV) genomic RNA is regulated by the internal ribosome entry site in the 5'-untranslated region (5'UTR) along with a short segment of the core gene sequence, the cis-acting replication element in the NS5B coding region and by the entire 3'UTR. Binding sites for eIF3 and 40S were marked. The start and stop codons for protein translation are marked by black squares, while two recognition sites on the 5'UTR for miR122 are marked by black rectangles; B: Polyprotein is co- and post-translationally cleaved by host or viral proteases to yield the structural proteins (core, E1 and E2) and the nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B proteins). Core, E1 and E2 are processed by cellular signal peptidase (filled arrowhead). Mature core protein will be generated after further cleavage by signal peptide peptidase (empty arrowhead)[317]. The NS2/NS3 junction site is cleaved by the NS2–NS3 auto-protease[318] (empty arrow), and the remaining nonstructural proteins are processed by the NS3/4A proteinase[319] (filled arrow); C: All of the HCV proteins are associated with endoplasmic reticulum directly or indirectly[320]; D: Then, NS3, NS4A, NS4B, NS5A and NS5B proteins will form the replication complex. Core and NS5A proteins will be transferred to lipid droplets, while E1 and E2 proteins will stay in the assembly sites. IRES: Internal ribosome entry site; 5'UTR: 5'-untranslated region.

Expression of the alternative reading frame/core+1 protein

In addition to the synthesis of HCV polyprotein, another viral protein is produced through the core+1 reading frame (for a review see References[151,152]). Recently, the conserved RNA stem loops (SLs) SL47 and SL87 of the HCV core gene were identified to possess a novel cis-acting element and direct the internal translation initiation of the alternative reading frame (ARF)/core+1[153].

RNA REPLICATION

HCV genomic RNA replication, tightly linked to ER membrane alterations designated the MW[154,155], occurs in the replication organelles (ROs)[156], mainly consisting of double membrane vesicles (DMVs)[157]. The HCV RNA replication requires at least viral genomic RNA and viral RNA-dependent RNA polymerase (NS5B protein) in the ROs. Thus, HCV RNA replication could be modulated by the viral RNA structure (*i.e.*, CREs), viral proteins (particularly, NS5B) and the biogenesis of ROs. Many cellular factors play important roles in the modulation of HCV RNA replication (for a review see References[158,159]).

The CREs of HCV genomic RNA were identified close to the 5'UTR and 3'UTR of the genome[160]. Several cellular proteins could bind to the 5'UTR and the 3'UTR of the viral RNA, facilitate the genome circularization and enhance RNA replication. These proteins include La[161], hnRNP L[162], the NFAR protein complex (NF90, NF45, and RHA)[163], PTB[164], PCBP2[137], and RNA binding protein 24[140]. High-mobility group box 1 interacting with SL 4 of 5'-UTR[165], Src-associated in mitosis 68 kDa protein binding with SL2 of 5'-UTR[166] and HSC70 with poly U/UC in the 3'-

UTR[167] could also promote HCV replication.

In addition to cellular proteins, liver-specific miR122 could bind to the two adjacent sites of HCV 5'UTR[168], forming a ternary complex[169]. Through this interaction, in addition to stimulating translation[128], miR122 could protect the genome from cellular DUSP11 pyrophosphatase activity[170] and subsequent degradation by the exonucleases Xrn1[171,172] and Xrn2[172,173] to facilitate RNA replication. Cellular proteins involved in HCV RNA replication through the regulation of miR122 include DDB1-Cul4 associate factor 1[174], glycogen synthase kinase 3b[175], GTPase Rab27a [176], heterogeneous ribonucleoprotein K (hnRNP K1)[177] and DEAD-box RNA helicase (DDX6)[178]. Interestingly, various miRNAs were found to compensate for the role of miR122 on HCV replication in non-hepatic cells[179].

The HCV nonstructural proteins, NS3 to NS5B, are required for RNA replication, and NS5B constitutes the catalytic core of the HCV replication complex[180,181]. Cellular protein kinase C-related kinase 2 could phosphorylate NS5B to regulate HCV RNA replication[182]. Several cellular factors were identified to enhance HCV RNA replication through interacting with NS5B, including cellular chaperonin TRiC/CCT [183], ribonucleotide reductase M2[184], sphingomyelin[185], HuR[186], VAPB-MSP [187] and CYP4F12[188].

In addition to NS5B, NS5A is also essential to HCV RNA replication. DDX3[189], Y-box binding protein 1[189] and FKBP6[190] could interact with NS5A to facilitate HCV RNA replication. Cellular cyclophilin A (CypA)[191,192] and human replication protein A[193] could bind to NS5A and stimulate the binding of NS5A to NS5B and viral RNA to facilitate HCV RNA replication. Three domains in NS5A protein were identified using biochemical analyses: Domain I (a.a. 1–213), domain II (a.a. 250–342) and domain III (a.a. 356–448) in NS5A[194]. Domain I, with RNA-binding ability, is essential for RNA replication[195], while domain III is required for assembly[196]. A critical ratio between the different phospho-forms of NS5A protein must be maintained for productive HCV RNA replication[197]. Several cellular kinases could phosphorylate HCV NS5A, including casein kinase II (CKII)[198] and CK1a[199], lipid kinase PI4KIIIα[200] and c-Abl tyrosine kinase[201]. These kinases control the switch between virus replication and assembly by phosphorylating NS5A[202]. Vinexin b also regulates HCV replication *via* modulating the phosphorylation status of NS5A in a CK1a-dependent manner[203]. Notably, association of vesicle-associated membrane protein A (VAP-A) with NS5A depends on the phosphorylation status of NS5A[204]: VAP-A binds to hypophosphorylated NS5A and contributes to HCV RNA replication [202]. F-box/LRR-repeat protein 2, when geranylgeranylated, could also interact with NS5A and promote HCV replication[205]. On the other hand, proprotein convertase subtilisin/kexin type 9 interacts with NS5A and inhibits HCV replication, possibly through preventing the dimerization of NS5A[206]. SPRY domain- and SOSC box-containing protein 2 induces NS5A ubiquitination and degradation to suppress HCV replication[207].

Viral NS3 protein is also an important component of HCV replication complex. Rad51[208] and GBF1[209] could interact with NS3 and promote HCV RNA replication.

HCV NS3–NS5B proteins, in collaboration with cellular factors, could induce MW formation. Among these viral proteins, NS5A and NS4B play a major role in the induction of MW[210,211]. Cellular factors could modulate HCV replication through affecting MW biogenesis. For example, CypA plays a role in the formation of DMVs through interacting with NS5A, in addition to its role in facilitating HCV RNA replication[212]. Similarly, receptor for activated protein C kinase 1 and ATG14L were found to participate in the DMV formation through interacting NS5A[213].

Proline–serine–threonine phosphatase interacting protein 2, a protein with membrane-deforming activity, is critical for MW formation through directly interacting with NS4B and NS5A[214]. Cytosolic phospholipase A2 gamma group IVC (PLA2G4C) is also required in the biogenesis of the MW. PLA2G4C expression was upregulated after HCV infection, contributing to HCV replication and assembly through interacting with NS5A and NS4B[215].

The cellular protein Surf4, maintaining ER-Golgi intermediate compartments and the Golgi compartment, was recruited into ROs by NS4B and was involved in the formation of DMVs[216]. Another cellular protein prolactin regulatory element binding could promote HCV RNA replication by interacting with NS4B and participating in the formation of DMVs[217].

HCV replication also depends on the GBF1-Arf1-COPI complex[218,219] and phosphatidic acid phosphatase lipin1[220], possibly due to their involvement in the MW biogenesis. Sphingomyelin and ceramide transfer protein (CERT), which is in the sphingomyelin biosynthesis pathway, are also essential for the biosynthesis of DMVs

[221].

Several Rabs (the Ras superfamily of small GTPases) are involved in the formation of HCV RNA replication machinery: (1) Rab5 can be recruited by NS4B and involved in HCV genome replication[222]; (2) Rab5 and 7 co-localize with NS4B and Rab2, 5 and 7 are required for HCV RNA replication[223]; (3) Rab1b and its negative regulator TBC1D20 are involved in the HCV replication[224,225]; and (4) Rab18, through associating with NS5A directly, is believed to promote the physical interaction between LDs and Ros[226].

Proteins in the nuclear transport machinery [including soluble nuclear transport factors, *e.g.*, karyopherins (Kaps)] and nucleoporins (Nups) in the nuclear pore complexes are involved in the HCV life cycle[227,228]. Interaction of various HCV proteins with Nups and Kaps could potentially alter host cell nucleocytoplasmic transport to facilitate HCV replication[229].

Several studies have demonstrated that autophagy plays an early role in establishing HCV re-plication[230,231]. Indeed, DMVs induced by HCV accumulate at the MW and morphologically resemble autophagosomes[232]. Thus, autophagy may help to induce the MW formation during HCV replication[233]. However, the role of autophagy in HCV replication is still a matter of controversy[234] (for a review see Reference[235]).

To shape an ER membrane into an RO requires not only viral and cellular proteins but also lipid synthesis (for a review see Refenence[236]). Many studies have shown that HCV could modulate lipid metabolism (*e.g.*, cholesterol and fatty acid biosynthesis) to promote viral replication[237-239]. Furthermore, to achieve robust HCV replication, it is necessary to limit the oxidative degradation of lipids[240]. Sphingolipid is also required for HCV replication and might contribute to detergent resistance of HCV replication sites[241]. Modulation of the lipid environment of RO by HCV includes the recruitment and activation of the lipid kinase PI4KIIIα by NS5A and NS5B proteins to generate enhanced levels of phosphatidylinositol 4-phosphate (PI4P) at the RO[200]. PI4P could attract lipid transport proteins [oxysterolbinding protein (OSBP), four-phosphate adaptor protein 2 and CERT)] to deliver glycosphingolipids, cholesterol and ceramide respectively to the RO[242,243]. OSBP and CERT could interact with the human VAP residing in the ER[244]. Both VAP-A and VAP-B, enriched in purified DMVs[245], interact with NS5A and NS5B and assist in the formation of the replicase complex[204,245]. Two types of lncRNAs, lin-IGF2-AS and lnc-7SK, are involved in HCV replication through regulating PI4P[246]. Recently, HCV NS3/4A protease was reported to control the activity of 24-dehydrocholesterol reductase, catalyzing the conversion of desmosterol to cholesterol, to regulate the lipid environment for HCV RNA replication[247].

FUSE binding protein 1 is reported to be an essential cellular factor required for HCV replication through inhibiting the function of tumor suppressor p53[248]. Several other cellular factors were involved in the HCV RNA replication, mTORC1[249] and chloride channel[250], but their exact roles are not yet defined.

VIRAL ASSEMBLY AND RELEASE

Assembly of HCV particles requires a viral genomic RNA, core proteins (for the capsid formation) and the viral envelope glycoproteins (E1 and E2). In addition to these viral factors, other viral nonstructural proteins and cellular factors, especially VLDL synthesis and secretion, are essential for the HCV assembly (for a review see Reference [251]).

Cleavage at the HCV core protein C-terminus by the intramembrane signal peptide peptidase is required for its maturation and targeting to LDs[252]. The mature core protein, forming the viral capsid, comprises two domains: The amino-terminal domain (D1; a.a. 1–118) and a central domain (D2; a.a. 119–177)[253]. D1 harbors basic aa residues that interact with viral RNA[254], while D2 is hydrophobic and associated with LDs[252]. LDs are important for the production of infectious HCV particles[255]. As expected, a reduction in the volume of LDs by the suppression of HSC70 expression[23] or disruption of LDs by the inhibitor of aryl hydrocarbon (AhR)[256] would inhibit HCV production. Thus, ADP-ribosylation factor-related protein 1 essential for LD growth is required for HCV propagation[257], while N-Myc Downstream-Regulated Gene 1 restricts HCV assembly by limiting LD formation[258].

Several cellular factors are involved in the association of the core with LDs. Diacylglycerol acyltransferase-1 (DGAT1) interacts with both the core and NS5A proteins and is required for the trafficking of these two proteins to LDs[259]. PLA2G4A also

plays a role in recruiting core to LDs, and its specific cleavage of lipids containing arachidonic acid is essential for the production of infectious viral particles[260]. Interaction of core and Nup98 in LDs is important for HCV propagation[22], while heterogeneous nuclear ribonucleoprotein K is recruited to sites in close proximity to LDs and suppress HCV production[261].

HCV genomic RNAs synthesized by the HCV replication complex (NS3–NS5B proteins) in the DMVs will be transferred by NS5A and NS3-4A proteins and encapsidated by the viral capsid to form the nucleocapsid. The HCV RNA structure [262] responsible for its encapsidation by core proteins has been suggested to be (1) a highly conserved secondary structure within the core D2 region[263]; (2) the conserved apical motifs of the 3'X region[264]; or (3) multiple RNA motifs with a secondary structure[265].

Lipid mobilization from cytoplasmic LDs favors the morphogenesis and secretion of HCV particles[266,267]. HCV infection suppresses the cellular lysophosphatidylcholine acyltransferase 1 expression resulting in altered lipid metabolism and, in turn, increases the production of infectious viral particles with low density[267]. α/β hydrolase domain-containing protein 5/CGI-58[266] and ATGL lipase[268] also mobilize lipids in LDs for the production of HCV particles.

PLA2G4C[215] and AAM-B[269] recruit the NS4B protein to LDs. Thus, these two proteins may bridge the steps of HCV RNA replication and assembly by translocation of RCs to LDs. In addition to DGAT1, CD2AP also participates in the transfer of NS5A to LDs[270]. Interactions between NS5A and core proteins are crucial for productive HCV infection[271]. Protein kinase C and CK substrate in neurons protein 2[272] and cortactin[273] promote interactions between HCV core and NS5A in the LDs. HCV NS5A protein domain I interacts with the D1 region of core protein[274]. Indeed, core and NS5A proteins are found associated with LDs at 12 h post-infection[275]. The LDs associated with core and NS5A proteins are close to the DMVs and the assembly sites on the ER membrane (Figure 4). Several studies suggested that the NS5A protein might link DMVs with assembly sites. Two LD-associated proteins, Rab18[226] and TIP47[276,277], were found to interact with NS5A and might help the juxtaposition of replication and assembly sites.

Formation of HCV nucleocapsid may occur in the LDs and/or assembly sites (Figure 4). Then, HCV nucleocapsid will move to the assembly sites and interact with viral E1/E2 proteins (envelopment) and bud into the ER lumen (egress) (Figure 4). All viral proteins are involved in HCV assembly[278,279]. The core and E1/E2 proteins are the integral protein components of an HCV particle. The other viral proteins do help viral assembly and egress, especially NS5A, p7, and NS2[278-281]. NS2, ubiquitinated by MARCH8[282], is a key regulator of viral assembly by bringing together the structural and nonstructural proteins required for particle formation. The cellular signal peptidase complex subunit 1 interacts with both NS2 and E2 proteins and mediates membrane association of the NS2–E2 complex to control HCV assembly [283]. Then, PLA1A plays a role in bridging NS2–E2 complex and NS5A-associated replication complex through its interaction with E2, NS2 and NS5A[284,285]. It is likely that NS2 protein brings E1, E2, NS3, NS5A and core proteins together to form a complex within the detergent-resistant membranes in the ER as an assembly platform to initiate HCV assembly[286]. Meanwhile, the clathrin Adaptor Related Protein Complex 2 Subunit Mu 1[287] and a small GTPase, Rab32[288], may transfer nucleocapsids to the sites of envelopment. HRS (hepatocyte growth factor-regulated tyrosine kinase substrate), an endosomal-sorting complex required for transport (ESCRT)-0 complex component, is involved in the viral envelopment[289].

HCV assembly and envelopment are linked to the VLDL synthesis and secretion [290]. Indeed, CIDEB, an important regulator of the VLDL pathway, contributes to the HCV assembly through interacting with NS5A[291]. However, inhibitors of microsomal triglyceride transfer protein (MTTP) affect secretion of HCV more severely than that of VLDL[292]. HCV is also reported to modify VLDL secretion[293,294]. These results suggest that HCV assembly occurs possibly through modification of the VLDL secretion. Indeed, colocalization of the core with Apo-E but not with Apo-B was demonstrated[295]. Therefore, it is more likely that HCV suppresses VLDL secretion and then uses the excess lipid to produce lipid-rich viral particles. Components of VLDL synthesis, such as MTTP[290], Apo-B[296] and especially Apo-E[10], have been implicated in HCV assembly. HCV production in HuH7 cells with double knockout of Apo-B/Apo-E was reduced significantly compared to that of single knockout cells, and ectopic expression of Apo-E in cells with double knockout of Apo-B/Apo-E restored production of infectious viruses. Furthermore, ectopic expression of Apo-E or MTTP in cells with double knockout of Apo-B/MTTP could restore infectious virus production[297]. These studies suggested that there are Apo-B-dependent and -

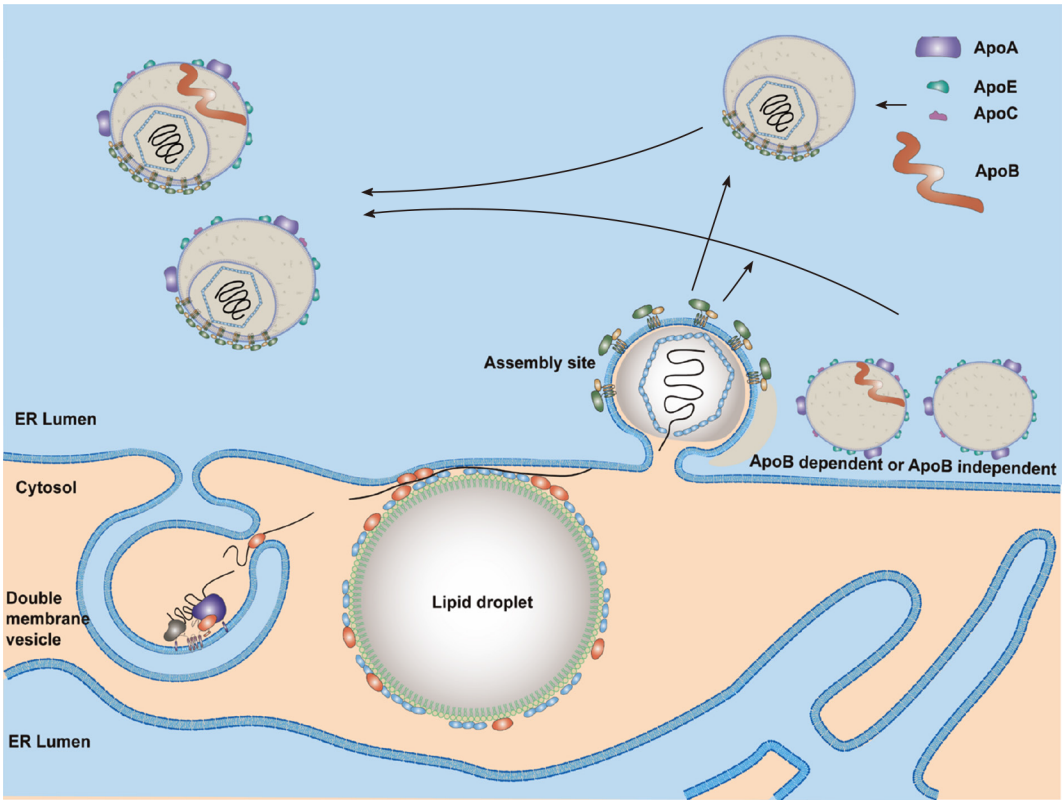

Figure 4 A proposed model for hepatitis C virus assembly. Lipid droplets (LDs) are surrounded by endoplasmic reticulum (ER)[321]. LDs with a hepatitis C virus (HCV) core and NS5A proteins are close to replication sites [double membrane vesicle (DMV)] and assembly sites. HCV genomic RNA synthesized by the replication complex (NS3–NS5B proteins) in the DMVs will be transferred by NS5A and NS3-4A proteins and encapsidated by the core proteins to form the nucleocapsid. Then, the HCV nucleocapsid will interact with glycoproteins E1/E2 in the assembly sites and bud into the ER lumen. Both Apo-B-dependent and -independent mechanisms are possibly involved in HCV particle assembly. One model shows the production of a fused form of HCV with very-low-density lipoproteins. Another model shows the budding of HCV particles with several apolipoproteins but not Apo-B. Nascent viral particles may be further lipidated by luminal lipoproteins and incorporated with exchangeable apolipoproteins. ER: Endoplasmic reticulum.

independent virus assembly pathways (Figure 4). Similar to the effect of ectopic expression of Apo-E in Apo-B/Apo-E double knockout cells, expression of exchangeable apolipoproteins (*e.g.*, Apo-A1, A2, C1, C2 and C3), the peptides of amphipathic α-helices containing the amino-terminal domain of Apo-E[297] or even human cathelicidin antimicrobial peptide[298] also restored infectious virus production. These results suggest that infectious virus production is regulated redundantly by exchangeable apolipoproteins expressed in the liver. Annexin A3 (ANXA3) through facilitating the incorporation of Apo-E[299] and Golgi protein 73, a resident Golgi membrane protein, through facilitating the interaction of HCV NS5A with Apo-E[300], promote HCV virion maturation. Recently, Apo-M, interacting with E2, was reported to be a novel virus particle-associated protein[301].

After envelopment, HCV particles then traffic to Golgi likely within COPII secretory vesicles[295,302]. Secretion of infectious HCV particles relies in part on components of the ESCRT pathway[303]. HCV egress but not VLDL secretion is blocked by silencing Rabs and the transGolgi network (TGN)-associating adaptors[304]. Moreover, inhibition of Apo-E secretion using monensin does not impair HCV release. These results suggested that HCV and VLDL use distinct secretion pathways[305]. Altogether, these results suggest that the release of HCV particles occur *via* a TGN-endosomal secretion pathway that is different from that of VLDL. The lipid-associated TM6SF2 (transmembrane 6 superfamily 2) has been demonstrated to promote lipidation and secretion of HCV particles[306]. The secreted HCV particle is likely a single particle fusion of viral structural proteins with various apolipoproteins and lipids (Figure 1).

Autophagy triggered by HCV-induced oxidative stress favors the release of HCV particles[307]. Thus, autophagy may play a role not only in the induction of DMVs but also in the secretion of HCV particles (for a review see Reference[235]).

HCV particles from the sera of HCV-infected patients harbor higher amounts of Apo-E than those derived from cell culture[308]. The interaction of Apo-E and HCV enhances specific infectivity and may aid HCV in evading neutralizing antibodies

[309]. HCV particles from the blood of HCV-infected patients contain Apo-B100 or Apo-B48, indicating that a significant fraction of HCV particles in blood is also associated with Apo-B48-containing lipoproteins[310]. These results suggested that the interactions between HCV particles and lipoproteins (*e.g.*, Apo-E and Apo-B48) in the blood of HCV patients (Figure 1B). Besides lipoproteins, specific serum factors, including albumin, also promote extracellular maturation of HCV particles[311].

Several cellular factors were involved in the assembly and secretion of HCV particles, such as ANXA2[312], sorcin (soluble resistance-related calcium-binding protein)[313], AP-1A, AP-1B, AP-4[101] and O-linked N-acetylglucosamine transferase [314], but their exact roles are not yet defined.

CONCLUSION

Study on the life cycle of the HCV has progressed tremendously after the development of *in vitro* HCV culture systems[315]. Understanding the HCV replication cycle led to the huge success of direct-acting anti-virals (DAAs) targeting NS3, NS5A, and NS5B. Hundreds of cellular factors involved in various stages of the HCV's life cycle have also been identified after more than 30 years of research on HCV–host cell interactions. Some of these cellular factors have been selected as targets for anti-HCV therapy (*e.g.*, SR-B1, EGFR, NPC1L1, miR122, CypA)[7]. Inhibitors against these cellular factors may complement existing DAAs. A successful vaccine for HCV is still a challenge in the near future. Understanding the mechanisms of viral entry, especially E2–CD81 interactions, should help in the development of a vaccine.

HCV particle, a hybrid lipo-viro-particle, does not look like a canonical enveloped virus. Thus, HCV has become a unique model for studying virus–host interactions, *e.g.*, between HCV and cellular lipid metabolisms. Furthermore, all positive-strand RNA viruses, including coronaviruses and picornaviruses, induce the reorganization of cellular membranes to replicate their genomes, similar to HCV[316]. Using HCV as a paradigm to study how HCV induces cellular membrane re-organization may lead to identification of broad-spectrum antivirals targeting cellular factors commonly used by these viruses.

Despite the impressive advances, many issues are still far from being clarified regarding HCV–host cell interactions. More studies are needed to understand the detailed mechanisms.

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