Host restriction factors for hepatitis C virus

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Core tip: Hepatitis C is a liver disease caused by the hepatitis C virus (HCV), which chronically infects approximately 130-150 million people. The ultimate outcome of HCV infection depends on host-viral interactions. Host cells encode multiple proteins to suppress HCV infection, known as host restriction factors. In this review, we will summarize the host restriction factors in different steps of the HCV life cycle. The possible mechanisms of the host restriction factors will also be discussed.

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Abstract

Host-hepatitis C virus (HCV) interactions have both informed fundamental concepts of viral replication and pathogenesis and provided novel insights into host cell biology. These findings are illustrated by the recent discovery of host-encoded factors that restrict HCV infection. In this review, we briefly discuss these restriction factors in different steps of HCV infection. In each case, we discuss how these restriction factors were identified, the mechanisms by which they inhibit HCV infection and their potential contribution to viral pathogenesis.

Key words: Hepatitis C virus; Host restriction factor; Interferon; Entry; Replication; Propagation

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INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver disease, with approximately 130-150 million people chronically infected[2]. Chronic HCV infection frequently develops into liver fibrosis, cirrhosis,
hepatocellular carcinoma (HCC), and eventually death[2]. Currently, there are two strategies for curing hepatitis C, including interferon (IFN)/ribavirin and direct-acting antiviral agents (DAAs)[3,4].

HCV is a single-stranded positive RNA enveloped virus that belongs to the family Flaviviridae. The viral RNA is 9.6 kb long and encodes a large polyprotein precursor of approximately 3000 amino acid residues. HCV polyprotein is proteolytically processed by cellular and viral proteases into structural (core, E1, and E2) and nonstructural (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins[5]. The majority of host-virus interactions are beneficial for the virus, including HCV[6]. Recently, a group of intracellular proteins/peptides that specifically evolved to interfere with HCV was identified. These proteins/peptides are collectively called host restriction factors[7,8]. Host restriction factors affect almost all stages of the HCV life cycle, including viral entry, replication, assembly and secretion. However, the involvement of these host restriction factors in the regulation of the HCV life cycle has not been fully elucidated. A better understanding of the interactions between HCV and host restriction factors will help to facilitate the identification of potential novel molecular targets for anti-HCV therapies.

IFNs belong to a family of cytokines that respond to external stimuli, such as viral infection[9]. IFNs activate the JAK-STAT signal amplification cascade and induce expression of a number of interferon stimulated genes (ISGs), including double-stranded RNA-dependent protein kinase R (PKR)[10], 2’,5’-oligoadenylate synthetase (OAS)[11], myxovirus resistance 1 (MxA)[12], and interferon-induced protein 56 (IFI-56K)[13]. However, for most ISGs, little is known regarding their specific targets or their modes of action.

The development of selectable subgenomic RNAs (replicons)[14], cell culture infection systems[15] and animal models has enabled the identification of ISGs responsible for suppressing HCV replication and their molecular mechanisms (Table 1). One strategy from Metz and coworkers involved identifying candidate genes up-regulated by IFNs in the HCV replicon system using cDNA microarray technology[16]. Next, they devised an siRNA-based rescue assay by individually knocking down each candidate gene in IFN-treated cells and screening for the subsequent restoration of HCV replication. Finally, overexpression of newly identified HCV restriction factors confirmed their antiviral activity[16]. In contrast to this RNA interference (RNAi)-based “loss of function” assay, “gain of function” studies can also be designed using an overexpression screening approach[17,18].

## RESTRICTION FACTORS IN HCV ENTRY

Some restriction factors have been shown to inhibit HCV entry, including interferon-induced transmembrane protein 1 (IFITM1)[19], ficolin-2[20] and ezrin-moesin-radixin (EMR) protein[21]. HCV E1 and E2 are viral envelope glycoproteins that mediate membrane fusion during virus uptake into hepatocytes[22]. HCV enters hepatocytes through a multi-step process that employs numerous host factors. Glycansaminoglycans[23,24] and low-density lipoprotein receptor (LDLR)[25] are thought to facilitate initial attachment, followed by interactions with CD81[26], scavenger receptor class B type 1 (SRBI)[27], the tight junction proteins claudin-1[28] and occludin[29], EGFR[30], the cholesterol uptake receptor Niemann-Pick C1-like 1[31], transferrin receptor 1[32] and the cell-death-inducing DFFA-like effector b (CIDE-B)[33].

The IFITM family proteins, including IFITM1, IFITM2 and IFITM3, have recently been shown to inhibit a number of viruses, including influenza A virus, SARS corona virus, West Nile virus and human immunodeficiency virus (HIV)[34-36]. IFITM1 was identified as a potential anti-HCV effector through a high-throughput genomics screen of ISGs, indicating a link between IFITM1 and its antiviral effects[37]. A previous study showed that IFITM1 restricts HCV replication, although the mechanism remains unclear[38]. A recent study defined IFITM1 as a hepatic tight junction protein and an ISG with activity against

| Host restriction factor | HCV life cycle step | IFN inducible or not | Ref. |
|------------------------|--------------------|---------------------|-----|
| IFITM1                 | Entry              | Y                   | [19]|
| IFITM1                 | Replication        | Y                   | [38]|
| Ficolin-2              | Entry              | N                   | [20]|
| EMR                    | Entry              | N                   | [21]|
| Moesin                 | Replication        | N                   | [21]|
| TRIM14                 | Replication        | Y                   | [16]|
| NSOS2                  | Replication        | Y                   | [16]|
| IFITM3                 | Replication        | Y                   | [16]|
| ISG56                  | Replication        | Y                   | [38]|
| Viperin                | Replication        | Y                   | [17,38,39]|
| CIDE-B                 | Replication        | N                   | [33,63]|
| Xmr1                   | Replication        | N                   | [66-70]|
| Xmr2                   | Replication        | N                   | [67,68]|
| APOBEC3G               | Replication        | N                   | [76,77]|
| Sac1                   | Replication        | N                   | [83,84]|
| ACBD3                  | Replication        | N                   | [91]|
| SOCS3                  | Replication        | N                   | [97]|
| MSR1                   | Replication        | N                   | [103]|
| BST-2                  | Particle production and release | Y | [125-127]|
| PKD                    | Secretion and release | N | [132]|
| YB-1                   | Particle production | N | [137,138]|

HCV: Hepatitis C virus; IFN: Interferon; IFITM1: Interferon-induced transmembrane protein 1; EMR: Ezrin-moesin-radixin; TRIM14: Tripartite motif containing 14; NSOS2: Nitric oxide synthase 2; IFITM3: Interferon-induced transmembrane protein 3; CIDE-B: Cell-death-inducing DFFA-like effector b; APOBEC3G: Apolipoprotein B messenger RNA-editing enzyme catalytic polypeptide-like 3G; ACBD3: Acyl-coenzyme A binding domain containing protein 3; SOCS3: Suppressor of cytokine signaling 3; BST-2: Bone marrow stromal cell antigen 2; PKD: Protein kinase D; YB-1: Y-box-binding protein 1.
HCV entry. IFITM1 can disrupt the coordination of HCV coreceptor interactions, including that of CD81 and occludin, to suppress viral entry[19].

Ficolin-2 (L-ficolin/p35) is a lectin-complement system activator that recognizes surface carbohydrates of microorganisms, and it plays an important role in innate immunity[20,21]. Ficolin-2 can specifically bind to N-glycans of the HCV envelope glycoproteins E1 and E2, which leads to activation of the lectin-complement pathway[22]. Recently, ficolin-2 was identified as a new HCV entry restriction factor regardless of the viral genotype[20]. Ficolin-2 blocks the attachment of HCV cell entry by interfering with HCVcc binding to the LDL and SR-B1 receptors and also weakly to the CD81 receptor. The C-terminal fibrinogen domain of ficolin-2 is the critical binding region of HCV-E1-E2. Ficolin-2 appears to bind to the HCV envelope surface glycoproteins E1 and E2 and inhibits HCV entry by blocking the interactions between HCV and LDLR, SR-B1, and CD81[20].

The ezrin-moesin-radixin (EMR) family includes closely related cytoskeletal regulatory proteins that regulate retroviral infection by modulating stable microtubule formation[42,43]. Chronic HCV infection-induced expression of moesin and radixin, but not ezrin, was found to be significantly decreased in Huh7.5 cells and liver biopsies from patients. This decrease in moesin and radixin was associated with an increase in stable microtubule formation. The EMR family differentially modulates HCV infection. CD81 engagement by HCV E2 induces spleen tyrosine kinase (SYK) phosphorylation[44]. SYK induces phosphorylation of ezrin/radixin and mostly likely modulates post-entry HCV trafficking towards the endoplasmic reticulum (ER). Only moesin plays a role in HCV RNA replication in the Con1 HCV replicon system[21].

RESTRICTION FACTORS IN HCV REPLICATION

After successful binding to a target cell, HCV penetrates the cell membrane and hijacks many host factors for the next step of its lifecycle. Although the HCV viral positive-strand RNA is translated on the endoplasmic reticulum, its RNA genome replicates within a ribonucleoprotein complex on ER-derived membranous structures termed the “membranous web”[45-47]. It is thought that the membranous structure is enriched in cholesterol[48] and unsaturated fatty acids[49]. NS3, NS4A, NS4B, NS5A and NS5B form the replicate complex, which is essential for viral RNA replication[44]. Here, we will summarize a series of host restriction factors suppressing the replication of HCV, such as tripartite motif containing 14 (TRIM14), nitric oxide synthase 2 (NOS2), IFITM3, ISG56, viperin, CIDEA, Xm1, Xm2, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G (APOBEC3G), Sac1, acyl-coenzyme A binding domain containing protein 3 (ACBD3), suppressor of cytokine signaling 3 (SOCS3), and class A scavenger receptor 1 (MSR1).

TRIM14, NOS2 and IFITM3 were identified as novel IFN-α and IFN-γ stimulated genes contributing to the suppression of HCV replication through an RNA interference (RNAi)-based “gain of function” screen[48]. Overexpression of each gene inhibited viral replication, whereas this inhibition was less efficient than that of IFN, indicating the IFN-induced antiviral effects against HCV are caused by the combined action of multiple ISGs. Raychoudhuri et al[49] recently showed that ISG56 (also known as IFIT1), which is induced in response to type I IFNs, also serves to restrict HCV infection. It was previously implicated in the antiviral action of IFNs against West Nile virus and LCMV[50], and it inhibits human HPV DNA replication by binding to the viral protein E1[51]. Transient expression of ISG56 suppresses subgenomic HCV RNA replication, whereas knockdown of ISG56 enhances HCV RNA replication[52,53].

Viperin is an evolutionarily conserved types I and II ISG[54]. Previous studies have suggested that viperin, in combination with other antiviral ISGs, has antiviral effects against HCV in vitro[55,56] and many other viruses, including human cytomegalovirus (HCMV)[57], yellow fever virus[58], influenza, alphaviruses, HIV and dengue[59]. Viperin localizes to both lipid droplets (LDs) and the ER, and the localization of viperin to LDs via its N-terminal amphipathic α-helix may reflect the mechanism that viperin uses to limit HCV replication[48]. Recent studies have found that viperin exerts its anti-HCV effect via its C-terminus. Viperin suppresses replication of HCV in both replicon and HCVcc systems, and it interacts with HCV NS5A via its C-terminal region at the LDs interface and within the HCV replication complex[17]. Moreover, viperin inhibits HCV replication, possibly through binding to VAP-A via its C-terminal region and interfering with its interaction with HCV NS5A[50].

The cell death-inducing DFFA-like effector (CIDE) family of proteins, including CIDEA, CIDEB, and CIDE/C-fat-specific protein 27, were initially identified based on their homology to the N-terminal domain of DNA fragmentation factors, and they were implicated in the induction of apoptosis[60]. Of these three members, CIDEA is expressed in liver tissue and regulates hepatic lipid homeostasis[61]. A potential interaction of CIDEA with the HCV protein NS2 was identified by a yeast-two hybrid assay[62]. Recently, CIDEA was suggested to be an essential cofactor in a late step of HCV entry, and it may facilitate membrane fusion between HCV and endosomes[33]. By contrast, Singaravelu and colleagues recently demonstrated that CIDEA can act as an anti-HCV host factor against HCV replication. They showed that HCV activates CIDEA expression in a human serum differentiated hepatoma cell line. CIDEA overexpression inhibits HCV replication, whereas siRNA-mediated knockdown of CIDEA expression promotes HCV replication and secretion of viral protein. Furthermore, CIDEA inhibits HCV
replication independently of its ability to regulate lipid metabolism. Interestingly, CIDEB-induced cell death and HCV inhibition occur in a caspase-independent manner\(^{63}\).

The cytoplasmic 5′-3′ exoribonuclease Xrn1 plays an important role in the 5′ exonucleolytic mRNA decay pathway, whereas the nuclear exoribonuclease Xrn2 possesses similar 5′ exoribonuclease activity and regulates RNA polymerase II transcription termination\(^{64,65}\). Recent studies have demonstrated that these two exoribonucleases are both responsible for the degradation of HCV RNA, against which miR-122 provides protection\(^{66-69}\). Xrn1 is a host restriction factor for all HCV strains tested, including JFH1, H77S.3, H77D and HJ3-5 viruses, but Xrn2 restricts the replication of only JFH1 and H77D\(^{67}\). Depletion of either Xrn1 or Xrn2 affects HCV RNA stability. Xrn1 depletion causes significant decay of JFH1 and HJ3-5 virus RNA, whereas Xrn2 depletion has a relatively modest effect on JFH RNA decay and has no effect on HJ3-5 RNA decay\(^{66-68}\). However, the 5′ UTR IRES element for translation of HCV and bovine viral diarrhea virus represses the cellular Xrn1 exoribonuclease. Repression of Xrn1 activity results in general repression of cellular mRNA decay and thus dysregulation of cellular gene expression, which may promote viral-induced cytopathology and pathogenesis\(^{70}\).

Human APOBEC3G (hA3G) belongs to the APOBEC superfamily. Substantial evidence indicates that hA3G is a cellular restriction factor for a group of viruses, including HIV-1, hepatitis B virus, T-cell leukemia virus type 1, and paroviruses\(^{71-75}\). Indeed, hA3G is also a host innate immunity factor for HCV infection. Introduction of external hA3G into HCV-infected Huh7.5 cells inhibits HCV replication, whereas treatment of HCV-infected Huh7.5 cells with specific hA3G siRNA enhances HCV replication. Stabilization of hA3G with RN-5 or IMB-2, two known hA3G stabilizers, effectively suppresses HCV replication\(^{76}\). The antiviral molecular mechanism of hA3G for HCV occurs through the direct binding of its C-terminus to the C-terminus of the HCV non-structural protein NS3, which leads to a decrease of NS3 helicase activity and inhibition of HCV replication; this differs from HIV-1\(^{77}\).

Sac1 is an evolutionarily conserved phosphatidylinositol phosphatase that dephosphorylates phosphatidylinositol-4-phosphate [PtdIns(4)P] and plays important roles at endoplasmic reticulum (ER)/plasma membrane contact sites and in Golgi localization, retention and trafficking\(^{78-80}\). Sac1 is an integral membrane protein and cycles continuously between the Golgi and ER via the canonical trafficking mechanisms involving coat protein complex I (COP-I) and COP- II\(^{81,82}\). Recent studies have uncovered the anti-HCV role of Sac1. Overexpression of Sac1 inhibits HCV replication\(^{83}\), whereas knockdown of Sac1 expression by siRNA significantly enhances HCV replication\(^{84}\). HCV NS5A hijacks the cellular factor ARFGAP1 (the GTPase-activating protein for ARF1) to remove the COP-I cargo Sac1 from the HCV replication area to maintain a PI4P-enriched microenvironment in favor of HCV replication\(^{84}\).

ACBD3, also known as GCP60 and PAP7, is a highly conserved Golgi protein involved in several signaling pathways and cellular regulation\(^{85}\). Recent work has demonstrated that ACBD3 functions as a novel interaction partner of PI4KB to regulate the replication of picornaviruses through a different mode of action, including members of the Enteroviruses (poliovirus, coxsackieviruses and human rhinoviruses) and Kobuviruses (Aichi virus)\(^{86-90}\). Moreover, ACBD3 exhibits a genotype-dependent antiviral role in HCV replication. Overexpression of GFP-ACBD3 was found to inhibit HCV replication, while knockdown of ACBD3 by siRNA clearly enhanced the core protein level in HCV-infected Huh7.5.1 cells. Furthermore, HCV NS5A co-localized with ACBD3, and NS5A from OR6 cells (GT1b) had higher binding affinity with ACBD3 than that from JFH1-infected Huh7.5.1 cells (GT2a). Moreover, NS5A competed with PI4KB for binding to ACBD3, and the colocalization efficiency between PI4KB and PI4P in OR6 cells (GT1b) was higher than that in JFH1-infected Huh7.5.1 cells (GT2a)\(^{91}\).

SOCS3 is a member of the SOCS (also known as JAB or SSI) family, and it acts in a negative feedback loop to regulate inflammatory responses and deactivate the JAK/STAT pathway. SOCS3 abolishes STAT3 phosphorylation and inhibits phospho-STAT1 expression, which impairs the IFN defense pathway\(^{92,93}\). Several groups have reported a role for SOCS3 during HCV infection. Among patients with chronic HCV infection, SOCS3 expression is significantly higher in patients nonresponsive to IFN treatment than in responders\(^{93-95}\). Bode et al\(^{96}\) found that the HCV core protein can induce SOCS3 expression and inhibit phospho-STAT1 expression to block the IFN-induced formation of ISGF3 in cell lines. Shao et al\(^{97}\) demonstrated that SOCS3 exhibits antiviral effects, downregulating HCV replication in an mTOR-dependent manner. SOCS3 overexpression in OR6 cells and JFH1-infected Huh7.5.1 cells suppresses HCV core protein levels and HCV replication despite the SOCS3-related inhibition of classical type I IFN signaling. Moreover, knockdown of SOCS3 enhances HCV protein and RNA levels. Furthermore, SOCS3 also downregulates mTOR expression, and inhibition of mTOR could reverse the inhibitory effects of SOCS3 on HCV replication\(^{97}\).

MSR1, also known as SCARA1, SR-AI, or CD204, is a macrophage-specific trimeric integral membrane glycoprotein that has been implicated in many macrophage-associated physiological and pathological processes, including Alzheimer’s disease, atherosclerosis and host defense. MSR1 can mediate the endocytosis of a range of ligands, such as acetylated LDL, bacterial cell wall constituents, and both ssRNA and dsRNA\(^{98-100}\). Recently, it was shown...
that MSR1 contributes to antiviral responses evoked by extracellular dsRNA. MSR1-deficient mice exhibit a marked decrease in mLDL uptake and increased susceptibility to infection by Listeria monocytogenes or herpes simplex virus type-1. MSR1 is required for induction of the Toll-like receptor 3 (TLR3)-mediated signaling that triggers pro-inflammatory responses in HCMV-exposed monocytes. MSR1 is also an essential component of TLR3 sensing that exerts an antiviral role in HCV infection. Knockdown of MSR1 blocks TLR3 sensing of HCV in infected cells, leading to increased cellular permissiveness to HCV infection. MSR1 mediates the establishment of a localized antiviral state in neighboring uninfected hepatocytes and restricts viral replication in cell culture. As a result, MSR1 limits the effect of HCV proteins that disrupt IFN responses in infected cells, restricting the spread of HCV in the human liver.

**RESTRICTION FACTORS IN HCV PROPAGATION**

The late stage of the HCV life cycle includes virus assembly, production and secretion. The HCV viral replication complex is assembled close to cytosolic lipid droplets (cLDs), and all viral proteins participate in this process. The core protein localizes around the cLDs, where it recruits the viral replication complex by core-NSA interaction. NS2 is also a key player of viral assembly that engages in crosstalk with both structural and nonstructural proteins. HCV particle production and secretion are tightly linked to cellular very low density lipoprotein components known as lipoviral particles (LVPs). LVPs consist of viral RNA, the capsid protein, envelop glycoproteins, cholesterol, triacylglycerol, apolipoprotein E (ApoE), ApoA1, ApoC1, ApoB, and microsomal triglyceride transfer protein. Although the HCV virion secretory pathway has not been completely characterized, it is believed to occur through the Golgi network, where HCV E1 and E2 glycoproteins undergo modifications. Multiple host factors are involved and hijacked by HCV to promote HCV assembly, production and secretion; few cellular factors have been found to restrict this process, including bone marrow stromal cell antigen 2 (BST-2), protein kinase D (PKD), Y-box-binding protein 1 (YB-1) and its partners.

Bone marrow stromal cell antigen 2 (BST-2, also known as tetherin, CD317, or HM1.24) is an IFN-induced glycosylated protein that is mainly localized to the cell membrane. It has recently been identified as a host restriction factor that inhibits the production and release of a wide range of enveloped viruses, including at least six virus families, Filoviridae (Ebola and Marburg viruses), retroviruses (HIV-1, HIV-2, lentiviruses, and simian immunodeficiency virus or SIV), Herpesviridae (Kaposi’s sarcoma-associated herpesvirus), Arenaviridae (Lassa fever virus), Rabdoviridae (vesicular stomatitis virus), and Paramyxoviridae (Sendai virus and Nipah virus). BST-2 tethers or traps budding virions on the cell surface to block their release, and they are subsequently endocytosed and degraded in lysosomes. As for HCV, it has also been demonstrated that BST-2 restricts its production and release in human hepatocytes, including HuH7.5.1 cells, primary human hepatocytes, and HepG2 cells. Atwood et al. found that overexpression of BST-2 by stimulation with all three types of IFNs significantly suppresses HCV production, whereas knockdown of endogenous BST-2 markedly enhances HCV production. Knockdown of BST-2 expression attenuates IFN-mediated anti-HCV activity, indicating that BST-2 is directly involved in IFN-mediated inhibition of HCV production.

Another group showed that HCV production is inhibited by BST-2 overexpression in a concentration-dependent manner.

PKD is a serine/threonine kinase including three isoforms, PKD1, PKD2, and PKD3. PKD is implicated in multiple intracellular processes and signaling pathways, such as vesicle trafficking, cell motility, cell adhesion and survival responses. PKD regulates the trafficking of secretory vesicles by promoting the fission of these vesicles from the trans-Golgi network to the plasma membrane. Recent work has shown that ceramide transfer protein (CERT) and oxysterol binding protein (OSBP), which are both phosphorylated by Golgi-associated PKD, play crucial roles in Golgi lipid trafficking and biogenesis. HCV maturation and secretion require sphingolipid biosynthesis, which also occurs in the Golgi and is affected by CERT and OSBP. Amako et al. found that PKD negatively regulates HCV secretion and/or release through the attenuation of CERT and OSBP function by phosphorylation inhibition. HCV infection downregulates PKD activation and subsequently impairs the secretory capacity of the host cell. PKD inhibition or downregulation promotes HCV secretion, whereas overexpression of a constitutively active form of PKD suppresses HCV secretion. Moreover, the suppressive effect of PKD on HCV secretion is subverted by the overexpression of nonphosphorylatable serine mutants of CERT (S132A) and OSBP (S240A). These observations indicate that the restrictive role of PKD in HCV secretion and/or release occurs through the Golgi network (Amako et al., 2011).

YB-1 belongs to a DNA/RNA-binding protein family, and it contains an evolutionary conserved cold-shock domain. It was originally identified as a transcription factor that specifically binds to the Y-box (an inverted CCAAT box) in the promoter region of MHC class I. Subsequently, it was found to be a major component of a ribonucleoprotein complex in the cytoplasm of mammalian cells and to participate in various cellular processes, including DNA repair, RNA transcription and splicing, mRNA packaging, exon skipping, drug
resistance and cancer progression\textsuperscript{135,136}. Using a powerful TAP approach and mass spectrometry, YB-1 was identified as a novel partner of NS3/4A and HCV genomic RNA. Importantly, knockdown of YB-1 expression impairs HCV RNA replication and unexpectedly stimulates HCV virus production and/or release. Moreover, HCV infection induces YB-1 redistribution to the surface of core-containing lipid droplets. These data show that YB-1 interacts with HCV NS3/4A, and it is involved in HCV replication and restricts HCV viral particle production\textsuperscript{137}. Recently, the same group demonstrated that the YB-1 ribonucleoprotein complex negatively regulates HCV virus production without affecting virus assembly in an NS3-dependent manner\textsuperscript{138}. They identified 71 YB-1-associated proteins using quantitative mass spectrometry. Among these candidates, they found a restrictive set of YB-1 partners, C1QBP, LARP-1, and IGFBP2, which redistribute to the surface of lipid droplets upon HCV infection and also restrain late steps of HCV particle production. Moreover, the NS3 Q221L mutant virus partially restores YB-1-dependent negative regulation upon particle production\textsuperscript{138}.

**CONCLUSION**

HCV triggers a wide variety of cellular responses in different stages of its life cycle through intricate interactions between viral and host proteins. Here, we have briefly reviewed host restriction factors for HCV that have emerged in recent years (Table 1). Although great progress has been made in resolving the host restriction factors and HCV's physical and functional networks, we have yet to understand how these factors protect hepatic cells from viral infection or how HCV possesses elaborate strategies to evade these restrictions. These intricate HCV restriction and counter-restriction mechanisms govern the ultimate outcome of HCV/cell infection. Powerful molecular virology tools and adequate experimental systems should be developed to further understand the molecular mechanisms underlying this delicate balance between restriction factors and HCV. A better understanding of this regulation may shed lights on more effective therapeutic approaches and may help to exploit the inhibitory properties of restriction factors to develop novel anti-HCV drugs and vaccines.

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