World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i4.1477

World J Gastroenterol 2016 January 28; 22(4): 1477-1486
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Hepatitis C Virus: Global view

Host restriction factors for hepatitis C virus

Li-Ya Zhou, Lei-Liang Zhang

Li-Ya Zhou, Lei-Liang Zhang, MOH Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100176, China

Author contributions: Zhou LY and Zhang LL analyzed the literature and wrote the manuscript.

Supported by National Natural Science Foundation of China, No. 81271832 and No. 81471955 to Zhang LL.

Conflict-of-interest statement: The authors declare no competing financial interests.

Correspondence to: Lei-Liang Zhang, PhD, MOH Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 9, Dongdan Santiao, Dongcheng District, Beijing 100730, China. armzhang@hotmail.com
Telephone: +86-10-67837355
Fax: +86-10-67837132

Received: April 28, 2015
Peer-review started: May 5, 2015
First decision: September 11, 2015
Revised: September 30, 2015
Accepted: November 13, 2015
Article in press: November 13, 2015
Published online: January 28, 2016

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

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.

Zhou LY, Zhang LL. Host restriction factors for hepatitis C virus. *World J Gastroenterol* 2016; 22(4): 1477-1486 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i4/1477.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i4.1477

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver disease, with approximately 130-150 million people chronically infected[1]. 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].

Table 1 Summary of host restriction factors for hepatitis C virus

Host restriction factor	HCV life cycle step	IFN induceble 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]
NOS2	Replication	Y	[16]
IFITM3	Replication	Y	[16]
ISG56	Replication	Y	[38]
Viperin	Replication	Y	[17,58,59]
CIDEB	Replication	N	[33,63]
Xrn1	Replication	N	[66-70]
Xrn2	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; NOS2: Nitric oxide synthase 2; IFITM3: Interferon-induced transmembrane protein 3; CIDEB: 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.

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. Glycosaminoglycans[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 (CIDEB)[33].

The IFITM family proteins, including IFITM, 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

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[39,40]. 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[41]. 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 SRBI 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 replicase complex, which is essential for viral RNA replication[14]. 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, CIDEB, Xrn1, Xrn2, 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[16]. 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*[38] 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[38].

Viperin is an evolutionarily conserved types Ⅰ and Ⅱ ISG[52]. Previous studies have suggested that viperin, in combination with other antiviral ISGs, has antiviral effects against HCV *in vitro*[53,54] and many other viruses, including human cytomegalovirus (HCMV)[55], yellow fever virus[56], influenza, alphaviruses, HIV and dengue[57]. 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[58]. 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[59].

The cell death-inducing DFFA-like effector (CIDE) family of proteins, including CIDEA, CIDEB, and CIDEC/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, CIDEB is expressed in liver tissue and regulates hepatic lipid homeostasis[61]. A potential interaction of CIDEB with the HCV protein NS2 was identified by a yeast-two hybrid assay[62]. Recently, CIDEB 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 CIDEB can act as an anti-HCV host factor against HCV replication. They showed that HCV activates CIDEB expression in a human serum differentiated hepatoma cell line. CIDEB overexpression inhibits HCV replication, whereas siRNA-mediated knockdown of CIDEB expression promotes HCV replication and secretion of viral protein. Furthermore, CIDEB 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 parvoviruses[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-26, 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 inactivate 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[98]. MSR1-deficient mice exhibit a marked decrease in mLDL uptake and increased susceptibility to infection by *Listeria monocytogenes* or herpes simplex virus type-1[101]. MSR1 is required for induction of the Toll-like receptor 3 (TLR3)-mediated signaling that triggers pro-inflammatory responses in HCMV-exposed monocytes[102]. 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[103].

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[104]. HCV particle production and secretion are tightly linked to cellular very low density lipoprotein components known as lipoviral particles (LVPs)[105]. LVPs consist of viral RNA, the capsid protein, envelop glycoproteins, cholesterol, triacylglycerol, apolipoprotein E (ApoE), ApoA1, ApoC1, ApoB, and microsomal triglyceride transfer protein[106-112]. 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[113,114]. 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)[115,116], retroviruses (HIV-1, HIV-2, lentiviruses, and simian immunodeficiency virus or SIV)[117,118], Herpesviridae (Kaposi's sarcoma-associated herpesvirus)[119], Arenaviridae (Lassa fever virus)[116], Rabdoviridae (vesicular stomatitis virus)[120,121], and Paramyxoviridae (Sendai virus and Nipah virus)[122]. BST-2 tethers or traps budding virions on the cell surface to block their release, and they are subsequently endocytosed and degraded in lysosomes[123,124]. 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[125-127]. Amet *et al*[125] 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[125]. Another group showed that HCV production is inhibited by BST-2 overexpression in a concentration-dependent manner[127].

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[128]. It regulates the trafficking of secretory vesicles by promoting the fission of these vesicles from the trans-Golgi network to the plasma membrane[129]. 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[130,131]. HCV maturation and secretion require sphingolipid biosynthesis, which also occurs in the Golgi and is affected by CERT and OSBP. Amako *et al*[132] 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*[132], 2011).

YB-1 belongs to a DNA/RNA-binding protein family, and it contains an evolutionary conserved cold-shock domain[133]. 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 Ⅱ[134]. 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[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[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[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 IGF2BP2, 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-complex-dependent negative regulation upon particle production[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.

REFERENCES

1 **Shepard CW**, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5**: 558-567 [PMID: 16122679 DOI: 10.1016/S1473-3099(05)70216-4]

2 **Yamane D**, McGivern DR, Masaki T, Lemon SM. Liver injury and disease pathogenesis in chronic hepatitis C. *Curr Top Microbiol Immunol* 2013; **369**: 263-288 [PMID: 23463205 DOI: 10.1007/978-3-642-27340-7_11]

3 **McHutchison JG**, Fried MW. Current therapy for hepatitis C: pegylated interferon and ribavirin. *Clin Liver Dis* 2003; **7**: 149-161 [PMID: 12691464]

4 **Pereira AA**, Jacobson IM. New and experimental therapies for HCV. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 403-411 [PMID: 19575025 DOI: 10.1038/nrgastro.2009.92]

5 **Moradpour D**, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol* 2007; **5**: 453-463 [PMID: 17487147 DOI: 10.1038/nrmicro1645]

6 **Lai CK**, Jeng KS, Machida K, Lai MM. Association of hepatitis C virus replication complexes with microtubules and actin filaments is dependent on the interaction of NS3 and NS5A. *J Virol* 2008; **82**: 8838-8848 [PMID: 18562541 DOI: 10.1128/JVI.00398-08]

7 **Bieniasz PD**. Intrinsic immunity: a front-line defense against viral attack. *Nat Immunol* 2004; **5**: 1109-1115 [PMID: 15496950 DOI: 10.1038/ni1125]

8 **Goff SP**. Genetic control of retrovirus susceptibility in mammalian cells. *Annu Rev Genet* 2004; **38**: 61-85 [PMID: 15568972 DOI: 10.1146/annurev.genet.38.072902.094136]

9 **Samuel CE**. Antiviral actions of interferons. *Clin Microbiol Rev* 2001; **14**: 778-809, table of contents [PMID: 11585785 DOI: 10.1128/CMR.14.4.778-809.2001]

10 **Clemens MJ**, Elia A. The double-stranded RNA-dependent protein kinase PKR: structure and function. *J Interferon Cytokine Res* 1997; **17**: 503-524 [PMID: 9335428]

11 **Silverman RH**. Fascination with 2-5A-dependent RNase: a unique enzyme that functions in interferon action. *J Interferon Res* 1994; **14**: 101-104 [PMID: 7523539]

12 **Stark GR**, Kerr IM, Williams BR, Silverman RH, Schreiber RD. How cells respond to interferons. *Annu Rev Biochem* 1998; **67**: 227-264 [PMID: 9759489 DOI: 10.1146/annurev.biochem.67.1.227]

13 **Guo J**, Peters KL, Sen GC. Induction of the human protein P56 by interferon, double-stranded RNA, or virus infection. *Virology* 2000; **267**: 209-219 [PMID: 10662616 DOI: 10.1006/viro.1999.0135]

14 **Lohmann V**, Körner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999; **285**: 110-113 [PMID: 10390360 DOI: 10.1126/science.285.5424.110]

15 **Lindenbach BD**, Evans MJ, Syder AJ, Wölk B, Tellinghuisen TL, Liu CC, Maruyama T, Hynes RO, Burton DR, McKeating JA, Rice CM. Complete replication of hepatitis C virus in cell culture. *Science* 2005; **309**: 623-626 [PMID: 15947137 DOI: 10.1126/science.1114016]

16 **Metz P**, Dazert E, Ruggieri A, Mazur J, Kaderali L, Kaul A, Zeuge U, Windisch MP, Trippler M, Lohmann V, Binder M, Frese M, Bartenschlager R. Identification of type I and type II interferon-induced effectors controlling hepatitis C virus replication. *Hepatology* 2012; **56**: 2082-2093 [PMID: 22711689 DOI: 10.1002/hep.25908]

17 **Helbig KJ**, Eyre NS, Yip E, Narayana S, Li K, Fiches G, McCartney EM, Jangra RK, Lemon SM, Beard MR. The antiviral protein viperin inhibits hepatitis C virus replication via interaction with nonstructural protein 5A. *Hepatology* 2011; **54**: 1506-1517 [PMID: 22045669 DOI: 10.1002/hep.24542]

18 **Schoggins JW**, Wilson SJ, Panis M, Murphy MY, Jones CT, Bieniasz P, Rice CM. A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature* 2011; **472**: 481-485 [PMID: 21478870 DOI: 10.1038/nature09907]

19 **Wilkins C**, Woodward J, Lau DT, Barnes A, Joyce M, McFarlane N, McKeating JA, Tyrrell DL, Gale M. IFITM1 is a tight junction protein that inhibits hepatitis C virus entry. *Hepatology* 2013; **57**: 461-469 [PMID: 22996292 DOI: 10.1002/hep.26066]

20 **Zhao Y**, Ren Y, Zhang X, Zhao P, Tao W, Zhong J, Li Q, Zhang XL. Ficolin-2 inhibits hepatitis C virus infection, whereas apolipoprotein E3 mediates viral immune escape. *J Immunol* 2014; **193**: 783-796 [PMID: 24928988 DOI: 10.4049/jimmunol.1302563]

21 **Bukong TN**, Kodys K, Szabo G. Human ezrin-moesin-radixin proteins modulate hepatitis C virus infection. *Hepatology* 2013; **58**: 1569-1579 [PMID: 23703860 DOI: 10.1002/hep.26500]

22 **Helle F**, Dubuisson J. Hepatitis C virus entry into host cells. *Cell Mol Life Sci* 2008; **65**: 100-112 [PMID: 17914604 DOI: 10.1007/

s00018-007-7291-8]
23 **Barth H**, Schafer C, Adah MI, Zhang F, Linhardt RJ, Toyoda H, Kinoshita-Toyoda A, Toida T, Van Kuppevelt TH, Depla E, Von Weizsacker F, Blum HE, Baumert TF. Cellular binding of hepatitis C virus envelope glycoprotein E2 requires cell surface heparan sulfate. *J Biol Chem* 2003; **278**: 41003-41012 [PMID: 12867431 DOI: 10.1074/jbc.M302267200]
24 **Germi R**, Crance JM, Garin D, Guimet J, Lortat-Jacob H, Ruigrok RW, Zarski JP, Drouet E. Cellular glycosaminoglycans and low density lipoprotein receptor are involved in hepatitis C virus adsorption. *J Med Virol* 2002; **68**: 206-215 [PMID: 12210409 DOI: 10.1002/jmv.10196]
25 **Agnello V**, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci USA* 1999; **96**: 12766-12771 [PMID: 10535997 DOI: 10.1073/pnas.96.22.12766]
26 **Pileri P**, Uematsu Y, Campagnoli S, Galli G, Falugi F, Petracca R, Weiner AJ, Houghton M, Rosa D, Grandi G, Abrignani S. Binding of hepatitis C virus to CD81. *Science* 1998; **282**: 938-941 [PMID: 9794763 DOI: 10.1126/science.282.5390.938]
27 **Scarselli E**, Ansuini H, Cerino R, Roccasecca RM, Acali S, Filocamo G, Traboni C, Nicosia A, Cortese R, Vitelli A. The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. *EMBO J* 2002; **21**: 5017-5025 [PMID: 12356718 DOI: 10.1093/emboj/cdf529]
28 **Evans MJ**, von Hahn T, Tscherne DM, Syder AJ, Panis M, Wölk B, Hatziioannou T, McKeating JA, Bieniasz PD, Rice CM. Claudin-1 is a hepatitis C virus co-receptor required for a late step in entry. *Nature* 2007; **446**: 801-805 [PMID: 17325668 DOI: 10.1038/nature05654]
29 **Ploss A**, Evans MJ, Gaysinskaya VA, Panis M, You H, de Jong YP, Rice CM. Human occludin is a hepatitis C virus entry factor required for infection of mouse cells. *Nature* 2009; **457**: 882-886 [PMID: 19182773 DOI: 10.1038/nature07684]
30 **Lupberger J**, Zeisel MB, Xiao F, Thumann C, Fofana I, Zona L, Davis C, Mee CJ, Turek M, Gorke S, Royer C, Fischer B, Zahid MN, Lavillette D, Fresquet J, Cosset FL, Rothenberg SM, Pietschmann T, Patel AH, Pessaux P, Doffoël M, Raffelsberger W, Poch O, McKeating JA, Brino L, Baumert TF. EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy. *Nat Med* 2011; **17**: 589-595 [PMID: 21516087 DOI: 10.1038/nm.2341]
31 **Sainz B**, Barretto N, Martin DN, Hiraga N, Imamura M, Hussain S, Marsh KA, Yu X, Chayama K, Alrefai WA, Uprichard SL. Identification of the Niemann-Pick C1-like 1 cholesterol absorption receptor as a new hepatitis C virus entry factor. *Nat Med* 2012; **18**: 281-285 [PMID: 22231557 DOI: 10.1038/nm.2581]
32 **Martin DN**, Uprichard SL. Identification of transferrin receptor 1 as a hepatitis C virus entry factor. *Proc Natl Acad Sci USA* 2013; **110**: 10777-10782 [PMID: 23754414 DOI: 10.1073/pnas.1301764110]
33 **Wu X**, Lee EM, Hammack C, Robotham JM, Basu M, Lang J, Brinton MA, Tang H. Cell death-inducing DFFA-like effector b is required for hepatitis C virus entry into hepatocytes. *J Virol* 2014; **88**: 8433-8444 [PMID: 24829338 DOI: 10.1128/JVI.00081-14]
34 **Brass AL**, Huang IC, Benita Y, John SP, Krishnan MN, Feeley EM, Ryan BJ, Weyer JL, van der Weyden L, Fikrig E, Adams DJ, Xavier RJ, Farzan M, Elledge SJ. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. *Cell* 2009; **139**: 1243-1254 [PMID: 20064371 DOI: 10.1016/j.cell.2009.12.017]
35 **Huang IC**, Bailey CC, Weyer JL, Radoshitzky SR, Becker MM, Chiang JJ, Brass AL, Ahmed AA, Chi X, Dong L, Longobardi LE, Boltz D, Kuhn JH, Elledge SJ, Bavari S, Denison MR, Choe H, Farzan M. Distinct patterns of IFITM-mediated restriction of filoviruses, SARS coronavirus, and influenza A virus. *PLoS Pathog* 2011; **7**: e1001258 [PMID: 21253575 DOI: 10.1371/journal.ppat.1001258]
36 **Lu J**, Pan Q, Rong L, He W, Liu SL, Liang C. The IFITM proteins inhibit HIV-1 infection. *J Virol* 2011; **85**: 2126-2137 [PMID: 21177806 DOI: 10.1128/JVI.01531-10]
37 **Erickson AK**, Gale M. Regulation of interferon production and innate antiviral immunity through translational control of IRF-7. *Cell Res* 2008; **18**: 433-435 [PMID: 18385680 DOI: 10.1038/cr.2008.46]
38 **Raychoudhuri A**, Shrivastava S, Steele R, Kim H, Ray R, Ray RB. ISG56 and IFITM1 proteins inhibit hepatitis C virus replication. *J Virol* 2011; **85**: 12881-12889 [PMID: 21976647 DOI: 10.1128/JVI.05633-11]
39 **Fujita T**, Matsushita M, Endo Y. The lectin-complement pathway--its role in innate immunity and evolution. *Immunol Rev* 2004; **198**: 185-202 [PMID: 15199963 DOI: 10.1111/j.0105-2896.2004.0123.x]
40 **Garlatti V**, Martin L, Lacroix M, Gout E, Arlaud GJ, Thielens NM, Gaboriaud C. Structural insights into the recognition properties of human ficolins. *J Innate Immun* 2010; **2**: 17-23 [PMID: 20375619 DOI: 10.1159/000233475]
41 **Liu J**, Ali MA, Shi Y, Zhao Y, Luo F, Yu J, Xiang T, Tang J, Li D, Hu Q, Ho W, Zhang X. Specifically binding of L-ficolin to N-glycans of HCV envelope glycoproteins E1 and E2 leads to complement activation. *Cell Mol Immunol* 2009; **6**: 235-244 [PMID: 19728924 DOI: 10.1038/cmi.2009.32]
42 **Haedicke J**, de Los Santos K, Goff SP, Naghavi MH. The Ezrin-radixin-moesin family member ezrin regulates stable microtubule formation and retroviral infection. *J Virol* 2008; **82**: 4665-4670 [PMID: 18305045 DOI: 10.1128/JVI.02403-07]
43 **Naghavi MH**, Valente S, Hatziioannou T, de Los Santos K, Wen Y, Mott C, Gundersen GG, Goff SP. Moesin regulates stable microtubule formation and limits retroviral infection in cultured cells. *EMBO J* 2007; **26**: 41-52 [PMID: 17170707 DOI: 10.1038/sj.emboj.7601475]
44 **Wack A**, Soldaini E, Tseng C, Nuti S, Klimpel G, Abrignani S. Binding of the hepatitis C virus envelope protein E2 to CD81 provides a co-stimulatory signal for human T cells. *Eur J Immunol* 2001; **31**: 166-175 [PMID: 11169450 DOI: 10.1002/1521-4141(200101)31:]
45 **Dubuisson J**, Penin F, Moradpour D. Interaction of hepatitis C virus proteins with host cell membranes and lipids. *Trends Cell Biol* 2002; **12**: 517-523 [PMID: 12446113 DOI: 10.1016/S0962-8924(02)02383-8]
46 **Gosert R**, Egger D, Lohmann V, Bartenschlager R, Blum HE, Bienz K, Moradpour D. Identification of the hepatitis C virus RNA replication complex in Huh-7 cells harboring subgenomic replicons. *J Virol* 2003; **77**: 5487-5492 [PMID: 12692249 DOI: 10.1128/JVI.77.9.5487-5492.2003]
47 **Penin F**, Dubuisson J, Rey FA, Moradpour D, Pawlotsky JM. Structural biology of hepatitis C virus. *Hepatology* 2004; **39**: 5-19 [PMID: 14752815 DOI: 10.1002/hep.20032]
48 **Paul D**, Hoppe S, Saher G, Krijnse-Locker J, Bartenschlager R. Morphological and biochemical characterization of the membranous hepatitis C virus replication compartment. *J Virol* 2013; **87**: 10612-10627 [PMID: 23885072 DOI: 10.1128/JVI.01370-13]
49 **Lyn RK**, Singaravelu R, Kargman S, O'Hara S, Chan H, Oballa R, Huang Z, Jones DM, Ridsdale A, Russell RS, Partridge AW, Pezacki JP. Stearoyl-CoA desaturase inhibition blocks formation of hepatitis C virus-induced specialized membranes. *Sci Rep* 2014; **4**: 4549 [PMID: 25008545 DOI: 10.1038/srep04549]
50 **Wacher C**, Müller M, Hofer MJ, Getts DR, Zabaras R, Ousman SS, Terenzi F, Sen GC, King NJ, Campbell IL. Coordinated regulation and widespread cellular expression of interferon-stimulated genes (ISG) ISG-49, ISG-54, and ISG-56 in the central nervous system after infection with distinct viruses. *J Virol* 2007; **81**: 860-871 [PMID: 17079283 DOI: 10.1128/JVI.01167-06]
51 **Terenzi F**, Saikia P, Sen GC. Interferon-inducible protein, P56, inhibits HPV DNA replication by binding to the viral protein E1. *EMBO J* 2008; **27**: 3311-3321 [PMID: 19008854 DOI: 10.1038/emboj.2008.241]
52 **Der SD**, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon alpha, beta, or gamma

using oligonucleotide arrays. *Proc Natl Acad Sci USA* 1998; **95**: 15623-15628 [PMID: 9861020 DOI: 10.1073/pnas.95.26.15623]
53 **Helbig KJ**, Lau DT, Semendric L, Harley HA, Beard MR. Analysis of ISG expression in chronic hepatitis C identifies viperin as a potential antiviral effector. *Hepatology* 2005; **42**: 702-710 [PMID: 16108059 DOI: 10.1002/hep.20844]
54 **Jiang D**, Guo H, Xu C, Chang J, Gu B, Wang L, Block TM, Guo JT. Identification of three interferon-inducible cellular enzymes that inhibit the replication of hepatitis C virus. *J Virol* 2008; **82**: 1665-1678 [PMID: 18077728 DOI: 10.1128/JVI.02113-07]
55 **Chin KC**, Cresswell P. Viperin (cig5), an IFN-inducible antiviral protein directly induced by human cytomegalovirus. *Proc Natl Acad Sci USA* 2001; **98**: 15125-15130 [PMID: 11752458 DOI: 10.1073/pnas.011593298]
56 **Khaiboullina SF**, Rizvanov AA, Holbrook MR, St Jeor S. Yellow fever virus strains Asibi and 17D-204 infect human umbilical cord endothelial cells and induce novel changes in gene expression. *Virology* 2005; **342**: 167-176 [PMID: 16150475 DOI: 10.1016/j.virol.2005.07.035]
57 **Fitzgerald KA**. The interferon inducible gene: Viperin. *J Interferon Cytokine Res* 2011; **31**: 131-135 [PMID: 21142818 DOI: 10.1089/jir.2010.0127]
58 **Hinson ER**, Cresswell P. The antiviral protein, viperin, localizes to lipid droplets via its N-terminal amphipathic alpha-helix. *Proc Natl Acad Sci USA* 2009; **106**: 20452-20457 [PMID: 19920176 DOI: 10.1073/pnas.0911679106]
59 **Wang S**, Wu X, Pan T, Song W, Wang Y, Zhang F, Yuan Z. Viperin inhibits hepatitis C virus replication by interfering with binding of NS5A to host protein hVAP-33. *J Gen Virol* 2012; **93**: 83-92 [PMID: 21957124 DOI: 10.1099/vir.0.033860-0]
60 **Xu L**, Zhou L, Li P. CIDE proteins and lipid metabolism. *Arterioscler Thromb Vasc Biol* 2012; **32**: 1094-1098 [PMID: 22517368 DOI: 10.1161/ATVBAHA.111.241489]
61 **Magnusson B**, Gummesson A, Glad CA, Goedecke JH, Jernås M, Lystig TC, Carlsson B, Fagerberg B, Carlsson LM, Svensson PA. Cell death-inducing DFF45-like effector C is reduced by caloric restriction and regulates adipocyte lipid metabolism. *Metabolism* 2008; **57**: 1307-1313 [PMID: 18702959 DOI: 10.1016/j.metabol]
62 **Erdtmann L**, Franck N, Lerat H, Le Seyec J, Gilot D, Cannie I, Gripon P, Hibner U, Guguen-Guillouzo C. The hepatitis C virus NS2 protein is an inhibitor of CIDE-B-induced apoptosis. *J Biol Chem* 2003; **278**: 18256-18264 [PMID: 12595532 DOI: 10.1074/jbc.M209732200]
63 **Singaravelu R**, Delcorde J, Lyn RK, Steenbergen RH, Jones DM, Tyrrell DL, Russell RS, Pezacki JP. Investigating the antiviral role of cell death-inducing DFF45-like effector B in HCV replication. *FEBS J* 2014; **281**: 3751-3765 [PMID: 24980280 DOI: 10.1111/febs.12901]
64 **Nagarajan VK**, Jones CI, Newbury SF, Green PJ. XRN 5'→3' exoribonucleases: structure, mechanisms and functions. *Biochim Biophys Acta* 2013; **1829**: 590-603 [PMID: 23517755 DOI: 10.1016/j.bbagrm.2013.03.005]
65 **West S**, Gromak N, Proudfoot NJ. Human 5' --> 3' exonuclease Xrn2 promotes transcription termination at co-transcriptional cleavage sites. *Nature* 2004; **432**: 522-525 [PMID: 15565158 DOI: 10.1038/nature03035]
66 **Li Y**, Masaki T, Yamane D, McGivern DR, Lemon SM. Competing and noncompeting activities of miR-122 and the 5' exonuclease Xrn1 in regulation of hepatitis C virus replication. *Proc Natl Acad Sci USA* 2013; **110**: 1881-1886 [PMID: 23248316 DOI: 10.1073/pnas.1213515110]
67 **Li Y**, Yamane D, Lemon SM. Dissecting the roles of the 5' exoribonucleases Xrn1 and Xrn2 in restricting hepatitis C virus replication. *J Virol* 2015; **89**: 4857-4865 [PMID: 25673723 DOI: 10.1128/JVI.03692-14]
68 **Sedano CD**, Sarnow P. Hepatitis C virus subverts liver-specific miR-122 to protect the viral genome from exoribonuclease Xrn2. *Cell Host Microbe* 2014; **16**: 257-264 [PMID: 25121753 DOI: 10.1016/j.chom.2014.07.006]
69 **Thibault PA**, Huys A, Amador-Cañizares Y, Gailius JE, Pinel DE, Wilson JA. Regulation of Hepatitis C Virus Genome Replication by Xrn1 and MicroRNA-122 Binding to Individual Sites in the 5' Untranslated Region. *J Virol* 2015; **89**: 6294-6311 [PMID: 25855736 DOI: 10.1128/JVI.03631-14]
70 **Moon SL**, Blackinton JG, Anderson JR, Dozier MK, Dodd BJ, Keene JD, Wilusz CJ, Bradrick SS, Wilusz J. XRN1 stalling in the 5' UTR of Hepatitis C virus and Bovine Viral Diarrhea virus is associated with dysregulated host mRNA stability. *PLoS Pathog* 2015; **11**: e1004708 [PMID: 25747802 DOI: 10.1371/journal.ppat.1004708]
71 **Bishop KN**, Verma M, Kim EY, Wolinsky SM, Malim MH. APOBEC3G inhibits elongation of HIV-1 reverse transcripts. *PLoS Pathog* 2008; **4**: e1000231 [PMID: 19057663 DOI: 10.1371/journal.ppat.1000231]
72 **Köck J**, Blum HE. Hypermutation of hepatitis B virus genomes by APOBEC3G, APOBEC3C and APOBEC3H. *J Gen Virol* 2008; **89**: 1184-1191 [PMID: 18420796 DOI: 10.1099/vir.0.83507-0]
73 **Lecossier D**, Bouchonnet F, Clavel F, Hance AJ. Hypermutation of HIV-1 DNA in the absence of the Vif protein. *Science* 2003; **300**: 1112 [PMID: 12750511 DOI: 10.1126/science.1083338]
74 **Narvaiza I**, Linfesty DC, Greener BN, Hakata Y, Pintel DJ, Logue E, Landau NR, Weitzman MD. Deaminase-independent inhibition of parvoviruses by the APOBEC3A cytidine deaminase. *PLoS Pathog* 2009; **5**: e1000439 [PMID: 19461882 DOI: 10.1371/journal.ppat.1000439]
75 **Sasada A**, Takaori-Kondo A, Shirakawa K, Kobayashi M, Abudu A, Hishizawa M, Imada K, Tanaka Y, Uchiyama T. APOBEC3G targets human T-cell leukemia virus type 1. *Retrovirology* 2005; **2**: 32 [PMID: 15943885 DOI: 10.1186/1742-4690-2-32]
76 **Peng ZG**, Zhao ZY, Li YP, Wang YP, Hao LH, Fan B, Li YH, Wang YM, Shan YQ, Han YX, Zhu YP, Li JR, You XF, Li ZR, Jiang JD. Host apolipoprotein B messenger RNA-editing enzyme catalytic polypeptide-like 3G is an innate defensive factor and drug target against hepatitis C virus. *Hepatology* 2011; **53**: 1080-1089 [PMID: 21480314 DOI: 10.1002/hep.24160]
77 **Zhu YP**, Peng ZG, Wu ZY, Li JR, Huang MH, Si SY, Jiang JD. Host APOBEC3G protein inhibits HCV replication through direct binding at NS3. *PLoS One* 2015; **10**: e0121608 [PMID: 25811715 DOI: 10.1371/journal.pone.0121608]
78 **Blagoveshchenskaya A**, Mayinger P. SAC1 lipid phosphatase and growth control of the secretory pathway. *Mol Biosyst* 2009; **5**: 36-42 [PMID: 19081929 DOI: 10.1039/b810979f]
79 **Liu Y**, Boukhelifa M, Tribble E, Morin-Kensicki E, Uetrecht A, Bear JE, Bankaitis VA. The Sac1 phosphoinositide phosphatase regulates Golgi membrane morphology and mitotic spindle organization in mammals. *Mol Biol Cell* 2008; **19**: 3080-3096 [PMID: 18480408 DOI: 10.1091/mbc.E07-12-1290]
80 **Liu Y**, Boukhelifa M, Tribble E, Morin-Kensicki E, Uetrecht A, Bear JE, Bankaitis VA. The Sac1 phosphoinositide phosphatase regulates Golgi membrane morphology and mitotic spindle organization in mammals. *Mol Biol Cell* 2008; **19**: 3080-3096 [PMID: 18480408 DOI: 10.1091/mbc.E07-12-1290]
81 **Rohde HM**, Cheong FY, Konrad G, Paiha K, Mayinger P, Boehmelt G. The human phosphatidylinositol phosphatase SAC1 interacts with the coatomer I complex. *J Biol Chem* 2003; **278**: 52689-52699 [PMID: 14527956 DOI: 10.1074/jbc.M307983200]
82 **Szul T**, Sztul E. COPII and COPI traffic at the ER-Golgi interface. *Physiology (Bethesda)* 2011; **26**: 348-364 [PMID: 22013193 DOI: 10.1152/physiol.00017.2011]
83 **Zhang L**, Hong Z, Lin W, Shao RX, Goto K, Hsu VW, Chung RT. ARF1 and GBF1 generate a PI4P-enriched environment supportive of hepatitis C virus replication. *PLoS One* 2012; **7**: e32135 [PMID: 22359663 DOI: 10.1371/journal.pone.0032135]
84 **Li H**, Yang X, Yang G, Hong Z, Zhou L, Yin P, Xiao Y, Chen L, Chung RT, Zhang L. Hepatitis C virus NS5A hijacks ARFGAP1 to maintain a phosphatidylinositol 4-phosphate-enriched microenvironment. *J Virol* 2014; **88**: 5956-5966 [PMID: 24623438 DOI: 10.1128/JVI.03738-13]
85 **Fan J**, Liu J, Culty M, Papadopoulos V. Acyl-coenzyme A binding domain containing 3 (ACBD3; PAP7; GCP60): an emerging

signaling molecule. *Prog Lipid Res* 2010; **49**: 218-234 [PMID: 20043945 DOI: 10.1016/j.plipres.2009.12.003]
86 **Dorobantu CM**, Ford-Siltz LA, Sittig SP, Lanke KH, Belov GA, van Kuppeveld FJ, van der Schaar HM. GBF1- and ACBD3-independent recruitment of PI4KIIIβ to replication sites by rhinovirus 3A proteins. *J Virol* 2015; **89**: 1913-1918 [PMID: 25410869 DOI: 10.1128/JVI.02830-14]
87 **Dorobantu CM**, van der Schaar HM, Ford LA, Strating JR, Ulferts R, Fang Y, Belov G, van Kuppeveld FJ. Recruitment of PI4KIIIβ to coxsackievirus B3 replication organelles is independent of ACBD3, GBF1, and Arf1. *J Virol* 2014; **88**: 2725-2736 [PMID: 24352456 DOI: 10.1128/JVI.03650-13]
88 **Greninger AL**, Knudsen GM, Betegon M, Burlingame AL, Derisi JL. The 3A protein from multiple picornaviruses utilizes the golgi adaptor protein ACBD3 to recruit PI4KIIIβ. *J Virol* 2012; **86**: 3605-3616 [PMID: 22258260 DOI: 10.1128/JVI.06778-11]
89 **Sasaki J**, Ishikawa K, Arita M, Taniguchi K. ACBD3-mediated recruitment of PI4KB to picornavirus RNA replication sites. *EMBO J* 2012; **31**: 754-766 [PMID: 22124328 DOI: 10.1038/emboj.2011.429]
90 **Téoulé F**, Brisac C, Pelletier I, Vidalain PO, Jégouic S, Mirabelli C, Bessaud M, Combelas N, Autret A, Tangy F, Delpeyroux F, Blondel B. The Golgi protein ACBD3, an interactor for poliovirus protein 3A, modulates poliovirus replication. *J Virol* 2013; **87**: 11031-11046 [PMID: 23926333 DOI: 10.1128/JVI.00304-13]
91 **Hong Z**, Yang X, Yang G, Zhang L. Hepatitis C virus NS5A competes with PI4KB for binding to ACBD3 in a genotype-dependent manner. *Antiviral Res* 2014; **107**: 50-55 [PMID: 24792752 DOI: 10.1016/j.antiviral.2014.04.012]
92 **Cui Q**, Jiang W, Wang Y, Lv C, Luo J, Zhang W, Lin F, Yin Y, Cai R, Wei P, Qian C. Transfer of suppressor of cytokine signaling 3 by an oncolytic adenovirus induces potential antitumor activities in hepatocellular carcinoma. *Hepatology* 2008; **47**: 105-112 [PMID: 17935223 DOI: 10.1002/hep.21951]
93 **Huang Y**, Feld JJ, Sapp RK, Nanda S, Lin JH, Blatt LM, Fried MW, Murthy K, Liang TJ. Defective hepatic response to interferon and activation of suppressor of cytokine signaling 3 in chronic hepatitis C. *Gastroenterology* 2007; **132**: 733-744 [PMID: 17258724 DOI: 10.1053/j.gastro.2006.11.045]
94 **Kim KA**, Lin W, Tai AW, Shao RX, Weinberg E, De Sa Borges CB, Bhan AK, Zheng H, Kamegaya Y, Chung RT. Hepatic SOCS3 expression is strongly associated with non-response to therapy and race in HCV and HCV/HIV infection. *J Hepatol* 2009; **50**: 705-711 [PMID: 19231005 DOI: 10.1016/j.jhep.2008.12.021]
95 **Walsh MJ**, Jonsson JR, Richardson MM, Lipka GM, Purdie DM, Clouston AD, Powell EE. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signalling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1. *Gut* 2006; **55**: 529-535 [PMID: 16299039 DOI: 10.1136/gut.2005.069674]
96 **Bode JG**, Ludwig S, Ehrhardt C, Albrecht U, Erhardt A, Schaper F, Heinrich PC, Häussinger D. IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. *FASEB J* 2003; **17**: 488-490 [PMID: 12551851 DOI: 10.1096/fj.02-0664fje]
97 **Shao RX**, Zhang L, Peng LF, Sun E, Chung WJ, Jang JY, Tsai WL, Hyppolite G, Chung RT. Suppressor of cytokine signaling 3 suppresses hepatitis C virus replication in an mTOR-dependent manner. *J Virol* 2010; **84**: 6060-6069 [PMID: 20375166 DOI: 10.1128/JVI.02484-09]
98 **DeWitte-Orr SJ**, Collins SE, Bauer CM, Bowdish DM, Mossman KL. An accessory to the 'Trinity': SR-As are essential pathogen sensors of extracellular dsRNA, mediating entry and leading to subsequent type I IFN responses. *PLoS Pathog* 2010; **6**: e1000829 [PMID: 20360967 DOI: 10.1371/journal.ppat.1000829]
99 **Kodama T**, Freeman M, Rohrer L, Zabrecky J, Matsudaira P, Krieger M. Type I macrophage scavenger receptor contains alpha-helical and collagen-like coiled coils. *Nature* 1990; **343**: 531-535 [PMID: 2300204 DOI: 10.1038/343531a0]
100 **Limmon GV**, Arredouani M, McCann KL, Corn Minor RA, Kobzik L, Imani F. Scavenger receptor class-A is a novel cell surface receptor for double-stranded RNA. *FASEB J* 2008; **22**: 159-167 [PMID: 17709607 DOI: 10.1096/fj.07-8348com]
101 **Suzuki H**, Kurihara Y, Takeya M, Kamada N, Kataoka M, Jishage K, Ueda O, Sakaguchi H, Higashi T, Suzuki T, Takashima Y, Kawabe Y, Cynshi O, Wada Y, Honda M, Kurihara H, Aburatani H, Doi T, Matsumoto A, Azuma S, Noda T, Toyoda Y, Itakura H, Yazaki Y, Kodama T. A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. *Nature* 1997; **386**: 292-296 [PMID: 9069289 DOI: 10.1038/386292a0]
102 **Yew KH**, Carsten B, Harrison C. Scavenger receptor A1 is required for sensing HCMV by endosomal TLR-3/-9 in monocytic THP-1 cells. *Mol Immunol* 2010; **47**: 883-893 [PMID: 19914718 DOI: 10.1016/j.molimm.2009.10.009]
103 **Dansako H**, Yamane D, Welsch C, McGivern DR, Hu F, Kato N, Lemon SM. Class A scavenger receptor 1 (MSR1) restricts hepatitis C virus replication by mediating toll-like receptor 3 recognition of viral RNAs produced in neighboring cells. *PLoS Pathog* 2013; **9**: e1003345 [PMID: 23717201 DOI: 10.1371/journal.ppat.1003345]
104 **Paul D**, Madan V, Bartenschlager R. Hepatitis C virus RNA replication and assembly: living on the fat of the land. *Cell Host Microbe* 2014; **16**: 569-579 [PMID: 25525790 DOI: 10.1016/j.chom.2014.10.008]
105 **Jones DM**, McLauchlan J. Hepatitis C virus: assembly and release of virus particles. *J Biol Chem* 2010; **285**: 22733-22739 [PMID: 20457608 DOI: 10.1074/jbc.R110.133017]
106 **Bartenschlager R**, Penin F, Lohmann V, André P. Assembly of infectious hepatitis C virus particles. *Trends Microbiol* 2011; **19**: 95-103 [PMID: 21146993 DOI: 10.1016/j.tim.2010.11.005]
107 **Chang KS**, Jiang J, Cai Z, Luo G. Human apolipoprotein e is required for infectivity and production of hepatitis C virus in cell culture. *J Virol* 2007; **81**: 13783-13793 [PMID: 17913825 DOI: 10.1128/JVI.01091-07]
108 **Gastaminza P**, Cheng G, Wieland S, Zhong J, Liao W, Chisari FV. Cellular determinants of hepatitis C virus assembly, maturation, degradation, and secretion. *J Virol* 2008; **82**: 2120-2129 [PMID: 18077707 DOI: 10.1128/JVI.02053-07]
109 **Huang H**, Sun F, Owen DM, Li W, Chen Y, Gale M, Ye J. Hepatitis C virus production by human hepatocytes dependent on assembly and secretion of very low-density lipoproteins. *Proc Natl Acad Sci USA* 2007; **104**: 5848-5853 [PMID: 17376867 DOI: 10.1073/pnas.0700760104]
110 **Hueging K**, Doepke M, Vieyres G, Bankwitz D, Frentzen A, Doerrbecker J, Gumz F, Haid S, Wölk B, Kaderali L, Pietschmann T. Apolipoprotein E codetermines tissue tropism of hepatitis C virus and is crucial for viral cell-to-cell transmission by contributing to a postenvelopment step of assembly. *J Virol* 2014; **88**: 1433-1446 [PMID: 24173232 DOI: 10.1128/JVI.01815-13]
111 **Lee JY**, Acosta EG, Stoeck IK, Long G, Hiet MS, Mueller B, Fackler OT, Kallis S, Bartenschlager R. Apolipoprotein E likely contributes to a maturation step of infectious hepatitis C virus particles and interacts with viral envelope glycoproteins. *J Virol* 2014; **88**: 12422-12437 [PMID: 25122793 DOI: 10.1128/JVI.01660-14]
112 **Meunier JC**, Russell RS, Engle RE, Faulk KN, Purcell RH, Emerson SU. Apolipoprotein c1 association with hepatitis C virus. *J Virol* 2008; **82**: 9647-9656 [PMID: 18667498 DOI: 10.1128/JVI.00914-08]
113 **Gusarova V**, Seo J, Sullivan ML, Watkins SC, Brodsky JL, Fisher EA. Golgi-associated maturation of very low density lipoproteins involves conformational changes in apolipoprotein B, but is not dependent on apolipoprotein E. *J Biol Chem* 2007; **282**: 19453-19462 [PMID: 17500069 DOI: 10.1074/jbc.M700475200]
114 **Vieyres G**, Dubuisson J, Pietschmann T. Incorporation of hepatitis C virus E1 and E2 glycoproteins: the keystones on a peculiar virion. *Viruses* 2014; **6**: 1149-1187 [PMID: 24618856 DOI: 10.3390/v6031149]
115 **Lopez LA**, Yang SJ, Hauser H, Exline CM, Haworth KG, Oldenburg J, Cannon PM. Ebola virus glycoprotein counteracts BST-2/Tetherin restriction in a sequence-independent manner

that does not require tetherin surface removal. *J Virol* 2010; **84**: 7243-7255 [PMID: 20444895 DOI: 10.1128/JVI.02636-09]
116 **Sakuma T**, Noda T, Urata S, Kawaoka Y, Yasuda J. Inhibition of Lassa and Marburg virus production by tetherin. *J Virol* 2009; **83**: 2382-2385 [PMID: 19091864 DOI: 10.1128/JVI.01607-08]
117 **Gupta RK**, Mlcochova P, Pelchen-Matthews A, Petit SJ, Mattiuzzo G, Pillay D, Takeuchi Y, Marsh M, Towers GJ. Simian immunodeficiency virus envelope glycoprotein counteracts tetherin/BST-2/CD317 by intracellular sequestration. *Proc Natl Acad Sci USA* 2009; **106**: 20889-20894 [PMID: 19864625 DOI: 10.1073/pnas.0907075106]
118 **Hauser H**, Lopez LA, Yang SJ, Oldenburg JE, Exline CM, Guatelli JC, Cannon PM. HIV-1 Vpu and HIV-2 Env counteract BST-2/tetherin by sequestration in a perinuclear compartment. *Retrovirology* 2010; **7**: 51 [PMID: 20529266 DOI: 10.1186/1742-4690-7-51]
119 **Pardieu C**, Vigan R, Wilson SJ, Calvi A, Zang T, Bieniasz P, Kellam P, Towers GJ, Neil SJ. The RING-CH ligase K5 antagonizes restriction of KSHV and HIV-1 particle release by mediating ubiquitin-dependent endosomal degradation of tetherin. *PLoS Pathog* 2010; **6**: e1000843 [PMID: 20419159 DOI: 10.1371/journal.ppat.1000843]
120 **Sarojini S**, Theofanis T, Reiss CS. Interferon-induced tetherin restricts vesicular stomatitis virus release in neurons. *DNA Cell Biol* 2011; **30**: 965-974 [PMID: 21919738 DOI: 10.1089/dna.2011.1384]
121 **Weidner JM**, Jiang D, Pan XB, Chang J, Block TM, Guo JT. Interferon-induced cell membrane proteins, IFITM3 and tetherin, inhibit vesicular stomatitis virus infection via distinct mechanisms. *J Virol* 2010; **84**: 12646-12657 [PMID: 20943977 DOI: 10.1128/JVI.01328-10]
122 **Kong WS**, Irie T, Yoshida A, Kawabata R, Kadoi T, Sakaguchi T. Inhibition of virus-like particle release of Sendai virus and Nipah virus, but not that of mumps virus, by tetherin/CD317/BST-2. *Hiroshima J Med Sci* 2012; **61**: 59-67 [PMID: 23077864]
123 **Neil SJ**, Zang T, Bieniasz PD. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* 2008; **451**: 425-430 [PMID: 18200009 DOI: 10.1038/nature06553]
124 **Yang H**, Wang J, Jia X, McNatt MW, Zang T, Pan B, Meng W, Wang HW, Bieniasz PD, Xiong Y. Structural insight into the mechanisms of enveloped virus tethering by tetherin. *Proc Natl Acad Sci USA* 2010; **107**: 18428-18432 [PMID: 20940320 DOI: 10.1073/pnas.1011485107]
125 **Amet T**, Byrd D, Hu N, Sun Q, Li F, Zhao Y, Hu S, Grantham A, Yu Q. BST-2 expression in human hepatocytes is inducible by all three types of interferons and restricts production of hepatitis C virus. *Curr Mol Med* 2014; **14**: 349-360 [PMID: 24236455 DOI: 10.2174/1566524013666131118111719]
126 **Dafa-Berger A**, Kuzmina A, Fassler M, Yitzhak-Asraf H, Shemer-Avni Y, Taube R. Modulation of hepatitis C virus release by the interferon-induced protein BST-2/tetherin. *Virology* 2012; **428**: 98-111 [PMID: 22520941 DOI: 10.1016/j.virol.2012.03.011]
127 **Pan XB**, Qu XW, Jiang D, Zhao XL, Han JC, Wei L. BST2/Tetherin inhibits hepatitis C virus production in human hepatoma cells. *Antiviral Res* 2013; **98**: 54-60 [PMID: 23422647 DOI: 10.1016/j.antiviral.2013.01.009]
128 **Fu Y**, Rubin CS. Protein kinase D: coupling extracellular stimuli to the regulation of cell physiology. *EMBO Rep* 2011; **12**: 785-796 [PMID: 21738220 DOI: 10.1038/embor.2011.139]
129 **Bossard C**, Bresson D, Polishchuk RS, Malhotra V. Dimeric PKD regulates membrane fission to form transport carriers at the TGN. *J Cell Biol* 2007; **179**: 1123-1131 [PMID: 18086912 DOI: 10.1083/jcb.200703166]
130 **Nhek S**, Ngo M, Yang X, Ng MM, Field SJ, Asara JM, Ridgway ND, Toker A. Regulation of oxysterol-binding protein Golgi localization through protein kinase D-mediated phosphorylation. *Mol Biol Cell* 2010; **21**: 2327-2337 [PMID: 20444975 DOI: 10.1091/mbc.E10-02-0090]
131 **Peretti D**, Dahan N, Shimoni E, Hirschberg K, Lev S. Coordinated lipid transfer between the endoplasmic reticulum and the Golgi complex requires the VAP proteins and is essential for Golgi-mediated transport. *Mol Biol Cell* 2008; **19**: 3871-3884 [PMID: 18614794 DOI: 10.1091/mbc.E08-05-0498]
132 **Amako Y**, Syed GH, Siddiqui A. Protein kinase D negatively regulates hepatitis C virus secretion through phosphorylation of oxysterol-binding protein and ceramide transfer protein. *J Biol Chem* 2011; **286**: 11265-11274 [PMID: 21285358 DOI: 10.1074/jbc.M110.182097]
133 **Wolffe AP**, Tafuri S, Ranjan M, Familari M. The Y-box factors: a family of nucleic acid binding proteins conserved from Escherichia coli to man. *New Biol* 1992; **4**: 290-298 [PMID: 1622927]
134 **Didier DK**, Schiffenbauer J, Woulfe SL, Zacheis M, Schwartz BD. Characterization of the cDNA encoding a protein binding to the major histocompatibility complex class II Y box. *Proc Natl Acad Sci USA* 1988; **85**: 7322-7326 [PMID: 3174636]
135 **Eliseeva IA**, Kim ER, Guryanov SG, Ovchinnikov LP, Lyabin DN. Y-box-binding protein 1 (YB-1) and its functions. *Biochemistry (Mosc)* 2011; **76**: 1402-1433 [PMID: 22339596 DOI: 10.1134/S0006297911130049]
136 **Kosnopfel C**, Sinnberg T, Schittek B. Y-box binding protein 1--a prognostic marker and target in tumour therapy. *Eur J Cell Biol* 2014; **93**: 61-70 [PMID: 24461929 DOI: 10.1016/j.ejcb.2013.11.007]
137 **Chatel-Chaix L**, Melançon P, Racine MÈ, Baril M, Lamarre D. Y-box-binding protein 1 interacts with hepatitis C virus NS3/4A and influences the equilibrium between viral RNA replication and infectious particle production. *J Virol* 2011; **85**: 11022-11037 [PMID: 21849455 DOI: 10.1128/JVI.00719-11]
138 **Chatel-Chaix L**, Germain MA, Motorina A, Bonneil É, Thibault P, Baril M, Lamarre D. A host YB-1 ribonucleoprotein complex is hijacked by hepatitis C virus for the control of NS3-dependent particle production. *J Virol* 2013; **87**: 11704-11720 [PMID: 23986595 DOI: 10.1128/JVI.01474-13]

P- Reviewer: Otsuka M **S- Editor**: Ma YJ **L- Editor**: Wang TQ
E- Editor: Zhang DN

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327
0 4>
9 771007 932045