Hepatitis C virus-host interactions: Etiopathogenesis and therapeutic strategies

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Abstract

Hepatitis C virus (HCV) is a significant health problem facing the world. This virus infects more than 170 million people worldwide and is considered the major cause of both acute and chronic hepatitis. Persons become infected mainly through parenteral exposure to infected material by blood transfusions or injections with nonsterile needles. Although the sexual behavior is considered as a high risk factor for HCV infection, the transmission of HCV infection through sexual means, is less frequently. Currently, the available treatment for patients with chronic HCV infection is interferon based therapies alone or in combination with ribavirin and protease inhibitors. Although a sustained virological response of patients to the applied therapy, a great portion of patients did not show any response. HCV infection is mostly associated with progressive liver diseases including fibrosis, cirrhosis and hepatocellular carcinoma. Although the focus of many patients and clinicians is sometimes limited to that problem, the natural history of HCV infection (HCV) is also associated with the development of several extrahepatic manifestations including dermatologic, rheumatologic, neurologic, and nephrologic complications, diabetes, arterial hypertension, autoantibodies and cryoglobulins. Despite the notion that HCV-mediated extrahepatic manifestations are credible, the mechanism of their modulation is not fully described in detail. Therefore, the understanding of the molecular mechanisms of HCV-induced alteration of intracellular signal transduction pathways, during the course of HCV infection, may offer novel therapeutic targets for HCV-associated both hepatic and extrahepatic manifestations. This review will elaborate the etiopathogenesis of HCV-host interactions and summarize the current knowledge of HCV-associated diseases and their possible therapeutic strategies.

Key words: Hepatitis C virus; Hepatocellular carcinoma; Extrahepatic; Signalling; Therapy

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INTRODUCTION

Hepatitis C virus (HCV) infects more than 170 million people worldwide\[^{1,2}\]. This virus is considered one of the major causes of both acute and chronic hepatitis. Persons become infected mainly through parenteral exposure to infected material by blood transfusions or injections with nonsterile needles. Although the sexual behavior is considered as a high risk factor for HCV infection, the transmission of HCV infection through sexual means, is less frequently\[^{3,4}\]. Besides the cause of liver disease, the natural history of HCV infection (HCV) is also associated with the development of several extrahepatic manifestations\[^{5-7}\]. Patients (40%-74%) infected with HCV might develop at least one extrahepatic manifestation during the course of the infection\[^{5-7}\]. HCV-associated liver diseases range from chronic hepatitis to fibrosis, cirrhosis and hepatocellular carcinoma (HCC)\[^{5}\]. Whereas, the extrahepatic manifestations include dermatologic, rheumatologic, neurologic, and nephrologic complications; and diabetes; arterial hypertension; autoantibodies and cryoglobulins\[^{5,8}\].

Currently, the available treatment for patients with chronic HCV infection is interferon based therapies alone or in combination with ribavirin. Although a sustained virological response of patients to the applied therapy, a great portion of patients did not show any response\[^{11}\]. Despite the mechanisms underlying the failure of interferon therapy are not well understood, several studies revealed that host response to interferon therapy is controlled by both viral and host factors\[^{10}\]. Therefore, the current knowledge obtained from the functional analysis of both viral- and host factors, during the infection might help for the development of a novel therapeutic strategy in the future.

HCV GENOME AND ITS FUNCTIONAL ORGANIZATION

HCV belongs to the family Flaviviridae and is a single positive strand of RNA (about 9.6 kb) and contains a long open reading frame flanked by both 5’ and 3’ untranslated regions that are important for both translation and replication processes of the viral RNA genome\[^{10,14}\]. Based on the sequence variation of HCV genome, six genotypes and more than 50 subtypes have been identified\[^{15,16}\]. The RNA genome of the virus encodes for a single polyprotein that is mainly processed by cellular and viral proteases into at least 10 structural (Core, E1, E2/p7) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins (Figure 1).

Proteins that are derived from the amino-terminal of the viral polyprotein are called viral structural proteins, these include core and two envelope glycoproteins, E1 and E2. HCV core is a basic protein with variable molecular weights (17-21 kDa) and is characterized by its RNA-binding activity that is thought to be responsible for the comprising of the viral nucleocapsid\[^{17,18}\]. However, the localization of HCV core protein in various subcellular compartments, including cytosol, lipid droplets, endoplasmic reticulum (ER), golgi apparatus, mitochondria, and nuclei suggests the contribution of HCV core protein in the modulation of different cellular processes\[^{20}\].

The two HCV envelope glycoproteins E1 and E2 interact with cell surface molecules including CD81, claudin-1, scavenger receptor class B type 1, and thereby facilitate the virus entry into the mammalian cells\[^{21,22}\]. HCV p7 protein is a small transmembrane protein that is characterized by its functional activity as an ion channel protein\[^{23}\]. In addition to the mentioned structural proteins, the non-structural protein NS2 is recognized to play a central role in polyprotein processing and virus assembly\[^{35}\].

HCV non-structural proteins (NS3, NS4A, NS4B, NS5A, and NS5B) are essential for both viral RNA replication and polyprotein processing\[^{25}\]. Besides its serine protease activity that is responsible for the cleavage of HCV polyprotein, and subsequently the generation of the amino termini of NS4A, NS4B, NS5A, and NS5B\[^{26}\], NS3 serves as an RNA helicase and NTPase, and is considered an essential component of the RNA replicase complex\[^{36-38}\]. NS4A, a small 54-amino-acid protein that forms a stable complex with the amino-terminal third of NS3, protease domain, and is required for a complete serine protease activity\[^{29}\]. NS4B, an integral membrane protein that is mostly localized on the cytoplasmic side of the ER membrane and is implicated in assembly of the replicase complex on lipid rafts\[^{30,31}\]. NS5A, a phosphoprotein that plays a role in viral resistance to interferon\[^{32,33}\]. NS5A also plays a role in RNA replication, and virus assembly\[^{34}\]. NS5B is the RNA-dependent RNA polymerase, and acts as the catalytic core of the macromolecular replicase complex essential for HCV RNA replication\[^{35,36}\].

The functional analysis of HCV genome using cloned HCV gene expression in mammalian cells, the development of subgenomic or full-length replicon derived from HCV, and the generation of infectious HCV genotypes 1a and 2a in human hepatocyte derived cell lines have significantly contributed to the advancement of HCV research\[^{37-39}\]. Recently, autophagy has gained importance as it plays an important role in HCV life cycle. Also, the role of HCV in the modulation of autophagy in hepatocytes has been reported\[^{40-43}\]. HCV may induce accumulation of autophagosomes via the induction of ER stress and the unfolded protein response\[^{40-43}\]. Similar to several viruses including poliovirus or coxsackieviruses, the induction of autophagosomes seems to play an important role in HCV replication\[^{40-43}\]. Taken together, the knowledge obtained from the functional analysis of the molecular mechanisms of HCV-induced autophagy in hepatocytes may help for the development of a therapeutic strategy for treatment of HCV infection.

INTERFERENCE OF HCV PROTEINS WITH INTRACELLULAR SIGNAL TRANSDUCTION PROCESSES

The most studied transmembrane and intracellular signal
transduction pathways, in the liver, are the mitogen-activated protein kinases (MAPKs), the transforming growth factor (TGF)-β, and the Janus kinase (JAK), tumor necrosis factor (TNF)-α and sphingolipid (SP). However, the activation of these signaling pathways by either cytokines or growth factors leads to the regulation of specific cellular processes including proliferation, growth, differentiation, adhesion, migration, apoptosis, and both synthesis and degradation of the extracellular matrix[44-47]. As recognized, the replication cycle of HCV is an intracellular mechanism that requires the intracellular signal transduction processes of the host cell to ensure genome replication, transcription and translation[48,49]. A proposed model for the interference of HCV with cellular signal transduction processes is demonstrated in Figure 2. 

MAPK signal transduction pathway

The legation of endothelial growth factor (EGF), hepatocyte growth factor (HGF) and TGF-α to their corresponding membrane receptors results mainly in the activation of the intrinsic tyrosine kinase that leads to ligand-receptor complex formation and subsequently autophosphorylation[50-52]. As a consequence, the formation of a transient complex from Ras proteins and GTP that subsequently mediates the activation of RAF and MAPKK kinases that, in turn, enhance the activation of MAPK by dual phosphorylation of threonine and tyrosine. Activated MAPK results in the phosphorylation of transcription factors such as cAMP response element-binding protein and Ets-related transcription factor 1 (ELK-1)[47,53-56]. Evolutionarily, MAPK signal transduction pathway is considered as one of the oldest signal transduction pathways in eukaryotic cells. This kinase contains three different signal pathways: the extracellular regulated protein kinase (ERK, p42/44 MAPK), the stress activated protein kinase [stress activated protein kinases (SAPK), p38 MAPK, p38-RK or p38], and the c-Jun N-terminal kinase (JNK, p64/54 SAPK). All of these pathways are implicated in the regulation of cellular processes including cell growth, differentiation, maturation, proliferation and apoptosis[53-63]. In mammalian cells every single pathway is activated by two mitogen-activated protein kinase kinase (MKK), e.g., JNK is activated by MKK4 and MKK7, ERK is activated by MKK1 and MKK2, whereas p38 is activated by MKK3 and MKK6[54,55,64]. However, the dual role of MKK in the activation of JNK, ERK or p38 signal transduction pathways still remains to be investigated in detail. Although ERK has been shown to play a

Figure 1  Hepatitis C virus genomic organization, replication, translation and generation of functional proteins. Proteins encoded by the hepatitis C virus (HCV) genome. HCV is formed by an enveloped particle harboring a plus-strand RNA of about 9.6 kb. The genome carries a long open-reading frame (ORF) encoding a polyprotein precursor of 3010 amino acids. Translation of the HCV ORF is directed via a 5’ nontranslated region (NTR) functioning as an internal ribosome entry site; it permits the direct binding of ribosomes in close proximity to the start codon of the ORF. The HCV polyprotein is cleaved co- and post-translationally by cellular and viral proteases into ten different products, with the structural proteins core (C), envelope 1 (E1) and envelope 2 (E2) located in the N-terminal third, whereas, the non-structural (NS2, NS3, NS4A, NS4B, NS5A, NS5B) replicative proteins are located in the remainder. Putative functions of the cleavage products are shown.
key role in the regeneration of liver cells, the role of p38, especially in hepatocytes regeneration, so far, is not clear. Physiologically, the activity of JNK in the liver is minimal, however, its increase during liver regeneration or HCV infection may result from the direct effect of the elevated level of hepatic TNF-α. Also, the promotion of cell proliferation in liver and non liver cells by HCV proteins is associated with the activation of MAP kinase signaling pathways JNK, p38 and ERK. An overview of HCV-induced alteration of MAP kinase signaling pathways is summarized in Figure 3.

**TGF-β signal transduction pathway**

TGF-β is a cytokine family member that plays a key role in the regulation of different cellular events including growth, differentiation, adhesion, apoptosis, and synthesis and degradation of the extracellular matrix. Although the elevation of TGF-β concentration is observed, during liver regeneration, no marked apoptosis was noted in hepatocytes. However, the inhibition of TGF-β-mediated apoptosis in hepatocytes may be linked with parallel augmentation of Smads, and other antipapoptotic proteins such as Bcl-2 and Bcl-X in hepatocytes.

In the liver, TGF-β is responsible for hepatocytes regeneration, the development of fibrosis, and HCC, as well as for the proliferation and differentiation of epithelial cells. Moreover, the elevation of TGF-β2 expression, in liver cells, during the course of HCV infection is associated with the development of neangiogenesis.

Also, the higher the concentration of both TGF-β1 and TGF-β2 in the sera of patients with chronic liver diseases, such as chronic HCV infection, the more severe the liver failure; an evidence for the association between the level of these cytokines and the development of liver diseases including hepatic fibrosis, cirrhosis and HCC. Simultaneously, in patients with chronic HCV, TGF-β1 serum concentration decreases and normalizes after successful antiviral therapy. However, the inhibition of TGF-β pathway during the infection with HCV, hepatitis B virus (HBV), adenoviruses or human papilloma virus (HPV) has been reported. Also, the mechanism whereby HCV protein NS5A inhibits the activity of TGF-β signal transduction pathway is reported. The inhibition of TGF-β pathway by HCV protein NS5A results from its direct reaction with its specific receptor.

TGF-β signaling pathway appears to be most prominent at the interface between development and cancer both in liver and gut epithelial cells. Since this signaling pathway is considered to play a pivotal role in the proliferation of embryogenic hepatocyte as well as in the formation of gastrointestinal cancers. In addition, many studies have reported a reduction of TGF-β receptors in...
The TNF-α and TNF-β receptors are extracellular transmembrane receptors that consist of extracellular, transmembrane, and intracellular [death domain (DD)] domains. TNFR1 is considered to play a key role in liver, and is expressed in hepatocytes as well as in kupffer cells and hepatic sinusoidal endothelial cells.[99-101]

Activated TNF-R1 binds, via the DD, to an adaptor protein TNFR-associated protein with DD, which afterwards activates Fas associated DD proteins, TNF associated factor 2 and receptor-interacting protein. All of these proteins influence different signal transduction pathways, which are involved in the regulation of apoptosis[94,95], and anti-apoptotic effects of TNF-α as the activation of nuclear factor kB (NF-kB) factor, as well as JNK and ERK from MAPK signal transduction pathway.[106]

Although the main target cells of HCV infection are the hepatocytes, the infection of B lymphocytes by HCV virus is documented[108]. Therefore, the participation of both innate and adaptive immune system at the etiopathogenesis of HCV during the course of HCV infection is expected.

The induction of TNF-α, during the infection with chronic HCV, results mainly in the activation of NF-kB pathway that subsequently stimulates transcription of genes encode for cytokines, acute phase proteins, immunoglobulins (Ig) and adhesion factors[88]. The ligation of TNF-α to TNF-R1, depending on the activated cellular proteins, leads to either cell proliferation or apoptosis[108].

TNF-α plays a diverse role in HCV infection. The activation of TNF-α has a pivotal role in the inflammatory process of chronic hepatitis C, and TNF-α levels correlate with the degree of inflammation[107,108].

HCV viral proteins including core, NS3 and NS4B protein have been reported to be involved in the modulation of cell proliferation[54,55,60,109,110] and production of proinflammatory cytokines TNF-α through NF-kB (Hassan et al[47,54,58], 2007), activator protein-1 (AP-1) and serum response element (SRE)[50]. AP-1 is a complex of homo- or heterodimers encoded by c-jun and c-fos family genes[59]. However, the ability of AP-1 to stimulate proliferation seems to be growth factors[47,111], oncogenes and inflammatory peptides- dependent mechanism[112]. SRE regulates the promoters of immediate early genes such as c-fos and PIP92. MAPK cascade activation phosphorylates Elk-1 factor binding with SRE and serum response factor[113]. Thus, the created complexes affect transcription of genes taking part in cell proliferation. A schematic view demonstrates HCV-mediated pathways leading to TNF-α production is outlined in Figure 5.

TNF-α signal transduction pathway
As recognized, macrophages, monocytes, mast cells and NK cells are the main source of TNF-α production that is considered to be one of the major mediators of the antiviral inflammatory response, which results in the enhancement of lymphocytes proliferation and differentiation, production of acute phase proteins and cell apoptosis[60,61].

The two essential TNF-α membrane receptors are the TNF-R1 and TNF-R2[99]. TNF-R1 is an extracellular transmembrane receptor that consists of extracellular, transmembrane and intracellular [death domain (DD)] domains. TNFR1 is considered to play a key role in liver, and is expressed in hepatocytes as well as in kupffer cells and hepatic sinusoidal endothelial cells[99-101].

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JAK signal transduction pathway
JAK signal transduction pathway can be activated by different cytokines and growth factors. This intracellular pathway operates in hepatocytes[114,115] as well as in immune[116], hematopoietic[117,118] and neural system cells[119]. After extracellular ligand-receptor interaction, receptor multimerization and the activation of JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2) is observed[120]. The receptor-
kinase complex phosphorylates cytoplasmic SH-2-containing transcription factors: signal transducers and activators of transcription (STATs). STATs are specifically inhibited by protein inhibitors of activated STAT and by suppressor of cytokine signaling (SOCS) through negative feedback control\[^{123}\]. SOCS proteins include SOCS1, 2, 3 and cytokine-induced Src homology 2 protein, which bind to JAK kinase inhibiting its enzymatic activity\[^{122}\]. STATs perform different, often opposing functions in the liver. STAT1 is mainly activated by interferon (IFN) type I (IFN-α/β) and IFN type II (IFN-γ). Its essential function in liver is the participation in antiviral immune defense, as well as in the development of inflammation and apoptosis. IFN-α/β and IFN-γ are ligands for STAT2, whose major function is antiviral defense. Membrane the IFN-α/β receptor (IFNAR) is a complex of two subunits: IFNAR1 and IFNAR2. IFNAR2 presents three diverse forms: full-length IFNAR2c is responsible for signal transduction and transcription process, whereas short form IFNAR2b and soluble form IFNAR2a inhibit these processes\[^{123}\]. The complex IFN-α/β - IFNAR activates JAK1 and Tyk2 kinases. IFN-γ takes effect by IFN-γ receptor (IFNGR): IFNGR1 and IFNGR2. STAT3 function is especially regulated by interleukin (IL)-6 and its family members such as cardiotrophin-1, oncostatin M, IL-11, leukemia inhibitory factor or ciliary neurotrophic factor, by IL-10, IL-22, EGF and HCV proteins. STAT3 participates in the acute phase response, stimulates hepatocytes regeneration and regulates lipid and carbohydrate metabolism in the liver\[^{124}\]. Moreover STAT3 is one of the main anti-HCV defense elements that act by increasing the IFN-α antiviral effect and by its direct cytoprotective and anti-inflammatory influence on hepatocytes\[^{125}\]. IL-6 and its related cytokines bind gp130 receptor protein, which plays a key role in liver regeneration.

Furthermore, the activation of gp130 is independent of the activation of other kinases, such as MAKP\[^{71}\]. The ligand-gp130 complex activates JAK1, JAK2 and Tyk2 and subsequently leads to the activation of STAT1-3. However, the modulation of JAK1, JAK2 and Tyk2-
mediated activation of STAT1-3 factors by HCV infection or by HCV structural and non-structural proteins has been demonstrated. Thus, the inhibition of the transmembrane and intracellular signal transduction pathways could be a new therapeutic target in chronic HCV treatment. HCV structural proteins Core, E2 and non-structural protein NS5A were reported to reduce the number of IFN-α receptors (IFN-α R1 and IFN-αR2c) and subsequently inhibit IFN-α-induced activation of STAT1-3[126-128]. As a result, viral replication, as well as inflammation and fibrosis in the liver, is augmented and has a negative effect on IFN-α treatment response among patients with severe liver damage. However, HCV does not affect IFN-γ function, and in consequence, STAT1 activation[129]. Moreover, the production of IFN-γ by NK cells during HCV infection is associated with the inhibition of hepatocytes regeneration[124]. Also, STAT4 has been shown to be activated by IL-12 and to play a critical role in hepatocytes damage during hepatic ischemia/reperfusion injury[130]. Whereas, STAT5 that is mainly activated by growth factors and involved in the regulation of the expression of genes encoding cytochrome P450, HGF and insulin growth factor 1, which are essential for hepatocytes metabolism, growth and differentiation[131,132]. STAT6 that is mainly regulated by IL-4, IL-12 and IL-13 and contributes in Th2 lymphocytes response during viral hepatitis and reduces hepatocytes damage during hepatic ischemia/reperfusion injury[133]. An overview demonstrating the interference of HCV with JAK/STAT, cytokines and IFN-associated pathways is outlined in Figure 6.

**SP signal transduction pathway**

Although SPs are considered to be the major components of eukaryotic plasma membranes and mediators of cell-to-cell interactions, their role as second messengers in transmembrane and intracellular signal transduction is documented[134]. The main function of the SP signal transduction pathway is the modulation of specific cell reactions including proliferation, growth arrest, differentiation, apoptosis and calcium homeostasis (Boyko et al[135], 2005). SP pathways can be activated by many pro-apoptotic and promitotic factors[136-138].

Ceramide is the most intensively studied second messenger of SP signal transduction pathway. Ceramide can mediate its antiproliferative effect by the activation of JNK, SAPK, c-Jun N-terminal kinase, c-Jun N-terminal kinase. An overview demonstrating its antiproliferative effects, ceramide has the ability to trigger mitochondrial dysfunction by the enhancement of reactive oxygen species (ROS) accumulation and cytochrome c release[140]. However, the antiapoptotic function of ceramide depends on its ability to decreases the intracellular level of anti-apoptotic proteins of the Bcl-2 family as well as the activity of anti-apoptotic enzymes such as Ca2+-kinases including protein kinase C (PKC), PKCζ and PKCβ/α/Akt[141]. Besides its role in the regulation of both cell survival and death, ceramide can also inhibit autophagocytosis by a mechanism based on the enhancement of apoptotic pathway[139,142]. As known, autophagocytosis is an intracellular process that relies on degradation of damaged, dead or used cell structures to prolong cell life[143].

Sphingosine (SFO) that is synthesized mainly from the hydrolysis of Ceramide by ceramidases is a member of the second messengers of SP signal transduction pathway. SFO plays a key role in promotion of apoptosis by the enhancement of ROS production in mitochondria and activation of caspase 3, 7 and 8[137]. Also, the inhibition of AKT by SFO leads to the augmentation of the cellular effects of both cytochrome c and caspase-3[137].

Besides its negative effect on DNA synthesis, methylation and replication, SFO reduces the activity of protein kinases including, PKC, calmodulin-dependent protein kinase and insulin receptor kinase[137], and thereby leads to disturbances of nuclear proteins phosphorylation including RNA polymerase, topoisomerase II, histones and matrix proteins[144].

Some studies underline the proliferative character of SFO suggesting that low cellular concentrations of SFO leads to stimulation of cell proliferation and DNA synthesis, whereas the high concentrations is associated with the induction of apoptosis. SFO-1-phosphate (SIP) that mainly synthesized from SFO, has been reported to have an anti-apoptotic potential[138]. An increase in the intracellular level of SIP can activate cell proliferation and its passing from G1 phase to S phase, augment the general number of cells resting in S phase, shorten the time needed for cell division, enhance survival rate of

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**Figure 5** A suggested model for hepatitis C virus-associated inflammation and the role of tumor necrosis factor α in the regulation of this mechanism. HCV: Hepatitis C virus; JNK: c-Jun N-terminal kinase; AP-1: Activator protein-1; NF-κB: Nuclear factor κB; PPAR: Peroxisome proliferator-activated receptor; TNF: Tumor necrosis factor; STAT: Signal transducers and activators of transcription.
cells subjected to pro-apoptotic factors, mobilize calcium ions from intracellular compartments, influence cytoskeletal architecture and the processes of cell migration and adhesion [14]. S1P modulates cell functions in two different ways: as an intracellular messenger and as a ligand of G protein-coupled receptors, known as endothelial differentiation genes (Edg) - Edg-1, -3, -5, -6 and -8 [14]. Cer can be phosphorylated by ceramide kinase to ceramide-1-phosphate (C1P), which can be dephosphorylated back to ceramide by C1P phosphatase [15]. Similarly to S1P, C1P promotes cell proliferation [15]. Recently, some studies have shown that the inhibition of SP metabolism can be a new therapeutic target for HCV infection [16].

**HCV-ASSOCIATED STEATOSIS**

Fatty liver (liver steatosis) is recognized as a histological phenotype of HCV infection that is occurring in all patients independent from the genotype [17,18]. Although the development of steatosis seems to be a direct consequence of viral protein expression, the molecular mechanism of its occurring appears to be genotype-specific [18].

The promotion of lipid homeostasis by HCV is mediated by the increasing of lipogenesis via a process including the activation of ER membrane bound transcription factors (SREBPs), reducing oxidation and lipid export [19]. As recognized, the main function of SREBPs is the regulation of the transcription of genes that encode for the enzymes which are essential for the biosynthesis of both cholesterol and fatty acid [20]. However, the suppression of both HCV replication and release in response to the inhibition of SREBP [21], or by the fatty acid synthase, an enzyme that is primarily involved in the biosynthesis of fatty acids [22,23], suggest that the host lipid metabolic pathways is considered a potential target for the treatment of HCV infection. A schematic view suggests HCV-mediated pathways leading to the development of steatosis are outlined in Figure 7.

**HCV-RELATED CRYOGLobulinEMIC**

Cryoglobulinemia is defined as the presence of circulating Ig that precipitate at temperatures below 37 °C and redissolve on rewarming [24]. Such an in vitro phenomenon is detectable in a wide number of chronic infectious and immunological disorders, as well as in some hematological malignancies [25].

Cryoglobulinemia is usually classified into serological subsets namely type I or monoclonal cryoimmunoglobulinemia that is composed by single monoclonal Ig, mixed cryoglobulinemia (MC) that contains a mixture of polyclonal IgG and monoclonal (type II) or polyclonal (type III) IgM rheumatoid factor (RF) [26]. Type I cryoglobulinemia is frequently associated with hematological disorder including multiple myeloma, immunocytoma or Waldenstrom’s macroglobulinemia, and is mostly asymptomatic except in the case of hyperviscosity syndrome [27,28]. Whereas, MC is characterized by a typical triad purpura, weakness, arthralgias as well as by multisystem organ involvement including chronic hepato-

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**Figure 6** Proposed model for the molecular mechanisms, which are involved in the regulation of hepatitis C virus-associated steatosis. HCV: Hepatitis C virus; ROS: Reactive oxygen species; PPAR: Peroxisome proliferator-activated receptor.
Figure 7  A schematic overview for the interference of hepatitis C virus with cytokines-associated Janus kinase/signal transducers and activators of transcription and cytokines-associated pathways. HCV: Hepatitis C virus; JAK: Janus kinase; EGFR: Endothelial growth factor receptor; IFN: Interferon; IFNR: IFN receptor; TRAF: Tumor necrosis factor associated factor; JAK: Janus kinase; SOCS: Suppressor of cytokine signaling; RIP: Receptor-interacting protein; ROS: Reactive oxygen species; STAT: Signal transducers and activators of transcription; NF-κB: Nuclear factor κB; IL: Interleukin; PPAR: Peroxisome proliferator-activated receptor.

When a role of HBV in another systemic vasculitis - the polyarteritis nodosa had been demonstrated\(^{[166]}\). However, soon after the identification of CV in patients with HBV infection\(^{[167]}\), the role of HCV in the development of CV has been considered\(^{[168,169]}\), the majority HCV patients was characterized by the presence of CV\(^{[170]}\), an evidence for the association between the chronic infection with HCV and the development of CV.

Currently, the role of HCV infection in the modulation of CV has been consequently established in several studies\(^{[160,169-172]}\). Therefore, a direct role for HCV in the formation of immune-complex-mediated vasculitis is considered. Besides its role as a main triggering factor of CV, HCV infection is thought to play an important role in the underlying lymphoproliferative disorder\(^{[160,169-172]}\). However, the detection of both active and latent HCV viral replication in the peripheral lymphocytes of patients with HCV infection and/or CV suggesting further a dual feature for HCV as both hepato- and lymphotropic virus\(^{[160,171]}\). Also, the affinity of lymphoid tissue to the infection with HCV supports further the occurring of both autoimmune and lymphoproliferative disorders in patients with chronic HCV infection\(^{[160,170-174]}\).

Although the HCV infection presents homogenous distribution worldwide, the geographical heterogeneity in the context of HCV-associated immune disorders is common\(^{[174]}\). Thus, the involvement of particular HCV genotypes, environmental and/or host genetic factors may play a central role in the development of HCV-associated CV.

Although the strong affinity of the HCV envelop protein E2 to CD81 and subsequently the modulation of immunological disorders\(^{[175]}\), the HCV, based on its biological features and several laboratory studies, seems to be insufficient to drive the different autoimmune-lymphoproliferative disorders in infected patients\(^{[173,174,175]}\). CD81 is a cell surface protein that expressed in both hepatocytes and B-lymphocytes\(^{[176]}\), and is recognized to play an important role by the entry of HCV particles\(^{[178]}\) in addition to the modulation of HCV-induced autoimmunity\(^{[179]}\). Therefore, the elevation of HCV-associated autoimmune diseases including CV during the course of infection\(^{[180,181]}\), may be a consequence of the interaction between HCV-E2 and CD81 leading the increase of the frequency of VDJ rearrangement in antigen-reactive B-cell\(^{[182]}\). Thus, the expansion of B-lymphocyte may be the main actor that is responsible for the observed autoantibody production during the course of HCV infection\(^{[174,182-184]}\). Also, another mechanisms including the molecular mimicry such as HCV antigens or host autoantgens may be involved in the activation of B lymphocyte and thereby increase the production of autoantibodies\(^{[168]}\).

In addition to its immunopathogeneity, HCV is reported to exert oncogenic potential that is mainly involved in the development of HCC\(^{[47,54,60,109,185]}\), and in the lymphomagenesis and, possibly, in other malignancies including thyroid cancer\(^{[44,186]}\). However, the modulation of TNF signaling of the host cells by HCV NS5A pro-
tein and the inhibition of JAK-STAT pathway by HCV core following the treatment with either IL-6 or IFN-γ stimuli\[126,130,138\], suggesting an important role for HCV in the dysregulation of the immune system.

The outcome and the severity of CV among patients are largely variable, also the behavior of the disease is mostly unpredictable and patient show usually a relatively benign clinical course. Thus, based on its complicated etiopathogenesis the treatment of CV syndrome must deal with the total clinical picture of the conflicting conditions including: HCV infection, autoimmune, and lymphoproliferative alterations\[164\]. Thus, according to the pathogenetic process leading to HCV infection and subsequently to the appearance of CV, the treatment of the disease may be applied at three different levels by means of etiologic, pathogenetic, and/or symptomatic therapies.

**DERMATOLOGIC MANIFESTATIONS OF HCV**

Dermatologic manifestations of HCV are classified, based on the disease to be proven, are either a suspected etiology or causation. The causal manifestation of the dermatologic diseases results from direct infection of HCV in the skin, lymphocytes, dendritic antigen-presenting cells, and blood vessels\[108\]. Whereas, the etiological manifestation of dermatological diseases results indirectly when the disruption of another organ infected or affected by HCV is associated with skin manifestations, but not specific or typical of skin responses in relation to HCV-infected or affected organ\[190,199\]. The causal manifestation is directly mediated by HCV infection as evidenced by the detection of HCV-RNA particles in epidermal cells\[191\] as well as by the induction of epitophenomena, that results mainly from the disruption of immune responses, in the skin of HCV-infected patients\[192,193\]. Also, the leukocytoclastic vasculitis that is due to cryoglobulinemia is considered a good evidence for a specific skin manifestation that results in a great part from the production of Ig, that is associated with rheumatoid characteristics causing an immune complex-mediated vasculitis and thereby presents a good example for etiologic skin manifestation\[194,195\]. Such skin responses result from a wide range of causes, for example the release of thyroid hormone in early HCV-linked autoimmune thyroiditis\[196,197\]. Also, chronic active hepatitis that mostly leads to fibrotic liver disease in patients with chronic hepatitis C infection can lead to the development of cutaneous vascular changes such as palmar erythema or spider nevus\[197,198\]. Moreover, arteriovenous hemangiomia, a benign acquired cutaneous vascular lesion, has been reported, in patients with chronic active hepatitis associated with HCV infection\[109\].

Another category of dermatologic manifestations in HCV infections includes porphyria cutanea tarda (PCT), an example for HCV-related disease in which causation is either unexplained or undeniable\[199\].

**HCV-ASSOCIATED LICHEN PLANUS**

Oral lichen planus (LP) is a chronic inflammatory condition that affects the oral mucous membranes with a variety of clinical presentations, including reticular papular, plaque-like, atrophic, and ulcerative lesions\[200\]. Oral LP affects about 0.1% to 4% of the population, it is a middle-aged disease that is more common among women\[202\]. The occurring of LP is induced by a wide range of factors including both bacterial and viral infections that thought to trigger the regulation of cell-mediated mechanisms leading the formation of oral LP lesions\[203,204\]. The association of LP with chronic liver disease is reported\[205\], and seems to be geographical dependent disease\[206\]. However, the risk of chronic liver disorders in LP patients appears to be age, sex, alcohol consumption and even hepatitis B infection (HBV)-independent\[207,208\]. Nevertheless, most patients with LP and chronic liver disease are not HBV\[209,210\] or hepatitis G virus-infected\[211,212\]. Although LP is rarely associated with various hepatic conditions such as Wilson’s disease, haemochromatosis, primary sclerosing cholangitis, and alpha-1-antitrypsin deficiency\[213\] the association of LP with primary biliary, and HCV infection is reported in several studies\[214,215\]. Thus, HCV-associated hepatic disease may precede LP onset or may be diagnosed together with it\[215\].

The geographic heterogeneity in the prevalence of HCV infection is reported in patients with other HCV-related extrahepatic conditions, such as serum autoantibodies, PCT or lymphoma\[216\], suggesting a genetic differences among the studied populations. Indeed, HCV-related oral LP seems to be associated mainly with the HLA-DR6 allele (Nagao et al\[226\], 1996) and this could partially explain the particularity of the geographic heterogeneity of HCV infection-associated LP. However, the pathogenetic link between LP and HCV is not fully understood, since the molecular mimicry between the virus and host epitopes is unexpected, and the viral factors including the genotype or the viral load\[227,228\]. Although the histological features of lesional tissue from HCV-positive or HCV-negative patients showed no substantial differences\[229,230\], the presence of HCV in oral LP lesional tissue becomes object of several investigations\[231,232,233\]. However, the presence of replicative intermediate HCV-RNA in LP specimens provide a strong evidence for the association between HCV infection and the development of LP in HCV infected patients\[232,230,233\]. Although, the compartmentalization of HCV in the oral mucosa, the infection with HCV does not seem to cause direct damage to epithelial cells in oral LP\[234\].

**HCV AND TYPE 2 DIABETES**

The epidemiological link between HCV and type 2 diabetes mellitus (T2DM) is common and widely reported\[235,236\], and the infection with HCV increase the risk of T2DM development\[237\]. Although the processes of T2DM development in patients with HCV infection is not fully described, the molecular mechanisms, which are
involved in the regulation of HCV-induced insulin resistance is studied in detail[240-243].

Chronic infection with HCV is mostly associated with insulin resistance that subsequently leads to the development of the metabolic disease T2DM. Thus, apart from the well-investigated complications of diabetes, the appearance of insulin resistance in patients with chronic HCV infection leads mostly to the enhancement of fibrosis, and cirrhosis, and in turn to the development of HCC[244]. Besides the liver complications, patients with insulin resistance show a poor response to antiviral therapy[245].

As known, insulin is an anabolic hormone that is secreted by pancreatic β-cells. This enzyme is essential for the maintenance of glucose homeostasis[246,247].

The pathway of insulin signaling pathway is involved mainly in the regulation of different cellular processes including the activation of insulin receptor (IR), IR substrates (IRS), phosphatidylinositol-3-kinase, Akt and PKC isoforms ζ and λ[248,249]. The activation of Akt promotes storage of excess glucose as glycogen by phosphorylating glycogen synthase kinase and subsequently suppresses gluconeogenesis by inhibition of phosphoenol-pyruvate carboxykinase and glucose-6 phosphatase. Whereas, the activation of Akt is involved in the translocation of the glucose transporter GLUT4 to the plasma membrane, and subsequently the enhancement of glucose uptake[250].

The direct interference of HCV with the insulin signaling cascade is experimentally documented in several studies[250]. Also, in patients with chronic hepatitis C, direct interactions between HCV and insulin signaling components occur and may result in insulin resistance, which in turn, may progress to T2D in at-risk individuals. In the transgenic mouse model[186], the core-encoding region of HCV is sufficient to induce IR. This effect was reversed by treatment with anti-TNF-antibodies, which suggested an increased level of serine phosphorylation of IRS-1 as induced by TNF-α. Thus, the core protein may induce IR indirectly via stimulation of the secretion of TNF-α. However, in vitro models suggest a direct interaction of the core protein with the insulin signaling pathway. An increased proteasome degradation of the IRS-1 and -2 via the activation of the SOCS-3[251]. Also, a genotype-specific mechanisms, in which down-regulation of peroxisome proliferator-activated receptor γ and up-regulation of SOCS-7 was observed in cells transfected with the core protein of genotype 3a[252]. A schematic view suggests HCV-mediated pathways leading to insulin resistance during the course of HCV infection is shown in Figure 8.

**CONCLUSION**

The replication cycle of HCV is host-dependent processes that require the intracellular signal transduction pathways of target cells to govern the nuclear factors, which are essential for the promotion of both transcriptional and translational mechanisms of the viral genome. Although the role of extracellular processes in the modulation of etiopathogenesis of HCV infection is not completely described, the role of intracellular signal transduction processes in the modulation of HCV-host interactions is established and seem to be the main actor in the regulation of HCV-associated both liver diseases and extrahepatic manifestations. The alteration of the physiological status of the intracellular signal transduction processes in response to their interaction with HCV viral proteins is thought to be responsible for the cause of the severe complications of chronic HCV infection including liver disease (e.g., hepatitis, fibrosis, cirrhosis and HCC) and extrahepatic manifestations (e.g., dermatologic, rheumatologic, neurologic, and nephrologic completions; and diabetes; arterial hypertension; autoantibodies and cryoglobulins).

Thus, the knowledge obtained from the functional analysis of the intracellular signal transduction processes using an HCV artificial cellular systems may help to identify a new therapeutic target for the treatment of chronic HCV infection and diseases.

Alterations in cellular proteins and their regulation during HCV infection are clearly involved in the development and progression of HCV-associated both hepatic and extrahepatic diseases.

Both host lipid metabolic and very low-density lipoproteins (VLDL) pathways play a central role in the regulation of different viral processes including replication, assembly, secretion and entry. Thus, the association of HCV with VLDL is thought to be a virus strategy
to evade host immune defense by masking the putative antigenic moieties from immune recognition. The understanding of the mechanistic details underlying the interactions between viral and host lipid metabolic pathways will help to identify potential host cell factors that may be required for HCV and the infectious processes and thereby gives the opportunity to design a potential therapeutic approach in order to eradicate HCV infection, and to decrease lipid metabolism-associated extrahepatic manifestation during the course of HCV.

The infection with HCV is more likely to favor IR in response to the accumulation of the viral proteins including core, NS3 and NS5A. However, the induction of IR by HCV infection is not merely because of glucose imbalances rather it involves upregulation of the glucogenetic and lipogenic genes that promote glucose intolerance and progresses towards IR, a step towards HCC.

As recognized, the development of HCC is mostly associated with activation of different signaling pathways including Ras/Raf/MAP kinase, cyclin/cyclin-dependent kinase and Wnt-1 pathways. The Constitutive expression of HCV viral proteins including core and NS3 results in a high basal activity of MAP kinase pathway and thereby potentiates hepatocyte transformation as well as the regulation of HGF, senescence and differentiation.

Also, HCV core protein can modulate the expression of cyclin-dependent inhibitor p21, which is considered the major target of p53 and triggers mainly the activities of cyclin/cyclin-dependent kinase complexes, which is implicated in cell-cycle control and tumor formation.

Moreover, the transcriptional upregulation of both Wnt-1 and its downstream target WISP-2 by HCV core protein suggested a possible role for Wnt-1 pathways in the modulation of HCV core and NS5A proteins in the development of HCC.

The functional analysis of JAK signal transduction pathway in the context of HCV-host interactions opened a new research option for a better understanding the mechanisms of HCV resistance to IFN-α therapy. JAK pathway is known to be the principal signaling pathway for IFN-α. Therefore, the inhibition of this pathway by viral proteins or by the reduction IFN-α receptors in response to the accumulation of both HCV structural (C and E2) and non-structural protein (NS5A) proteins may contribute to the resistant mechanisms of HCV to IFN therapy. Besides the negative effect on the virological response to IFN-α treatment, the reduction of IFN-α receptors plays a central role in the suppression of IFN-α-mediated activation of STAT1-3 and subsequently augments viral replication, inflammation and fibrosis during the course of HCV infection.

Therefore, the better understanding of the molecular mechanisms, which are involved in the regulation of virus-host cell interactions may help to develop a new therapeutic strategies. These therapeutic strategies may help to decrease or even to inhibit HCV-associated both hepatic and extrahepatic diseases, and make IFN-α therapy more effective in HCV-infected patients.

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