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TOPIC HIGHLIGHT

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Immunologic, metabolic and genetic factors in hepatitis C virus infection

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Abstract

The mechanisms that regulate disease progression during hepatitis C virus (HCV) infection and the response to treatment are not clearly identified. Numerous studies have demonstrated that a strong host immune response against HCV favors HCV clearance. In addition, genetic factors and metabolic machinery, particularly cholesterol modulation, are involved in HCV infection. It is likely that the interplay between all of these factors contributes to the outcome of HCV infection. In recent years, the world has experienced its largest epidemic of obesity. Mexico and the United States are the leading sufferers from this epidemic at the global level. Obesity is associated with the development of numerous pathologies including hypercholesterolemia which is one of the eight most important risk factors for mortality in Mexico. This may be related to the course of HCV infection in this population. Here, we focus on the urgent need to study the progression of HCV infection in relation to ethnic characteristics. Discoveries are discussed that hold promise in identifying immune, metabolic and genetic factors that, in conjunction, could be therapeutic targets or predictors of the progression of HCV infection.

Key words: Hepatitis C virus; Immune response; Lipids; Metabolism; Genetics

Core tip: Immunologic, metabolic and genetic factors are involved in the progression of hepatitis C virus (HCV) infection and the response to treatment. The significant increase in obesity worldwide, including in Mexico, imposes a new metabolic stress factor in patients with HCV infection. Given that the lipid components associated with HCV infection are finely modulated, it is possible that the progression of HCV infection may be regulated by the characteristics of the population's lipid composition.

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INTRODUCTION

Hepatitis C infection is caused by the hepatitis C virus

(HCV), a positive-stranded ribonucleic acid (RNA) virus of the *Flaviviridae* family with a hepatotropic lifecycle. HCV infection is an important cause of chronic liver disease and the third-leading cause of all death from cirrhosis and hepatocellular carcinoma (HCC) worldwide. Approximately 3% of the world's population (160 million people) are currently infected with HCV, which in most cases establishes a lifelong chronic infection[1]. However, 25%-30% of infected individuals spontaneously clear the virus during acute infection. Because HCV is a non-cytopathic virus, it is accepted that the interplay between the virus and the host immune response may influence the outcome of infection[2]. In addition, host genetic factors, such as polymorphisms in cytokine and chemokine receptor genes promoters[3,4], are thought to be important contributors to the modulation of HCV outcome.

A key role for the low-density lipoprotein receptor (LDL-R) has been demonstrated during the first steps of HCV attachment to the cell surface[5]. LDL is responsible for transporting most of the cholesterol in plasma[6] and cholesterol levels are tightly modulated during HCV infection. Virus entry into the cell is also mediated by other lipoprotein receptors including scavenger receptor class B type I (SRB- I). In addition to providing a docking site for HCV particles, SRB- I facilitates entry of the virus into the hepatocyte[6,7]. The E2 envelope protein determines viral attachment to SRB- I .

Currently, Latinos represent the fastest growing ethnic group in the United States and are the most overweight. Mexico and the United States are experiencing the largest obesity epidemic in the world. In conjunction, genetic and cultural components, lifestyle and environmental factors are all associated with the development of obesity. In addition to representing a public health problem by itself, obesity is also associated with the development of numerous pathologies, including hypercholesterolemia. A recent analysis of the burden of disease revealed that hypercholesterolemia was among the eight most important risk factors for mortality in Mexico[8]. Thus, the specific characteristics of the lipid components already described suggest a unique mechanism of regulation of metabolic machinery among the Mexican people that could impact the progression of HCV infection.

Crosstalk between metabolic and immune components in conjunction with viral and genetic host factors may occur and predict HCV disease outcome. To date, the exact mechanisms responsible for HCV clearance and recovery are unknown. An understanding of these mechanisms will contribute to the development of novel, individualized, preventive strategies and an urgently needed vaccine. This review summarizes recent advances in understanding the crosstalk between the immune response, metabolism and genetics in HCV viral clearance and emphasizes characteristics of the Mexican population and their association with this process.

IMMUNE RESPONSE TO HCV INFECTION

Innate and adaptive immune response to HCV

A robust innate immune response is activated when HCV infects the liver. This response includes the induction of several interferon-stimulated genes (ISGs)[9,10] and is mediated by the specific production of inflammatory and antiviral cytokines by macrophages, natural killer (NK) cells and neutrophils, which release perforin, granzyme B, interferon-gamma (IFN-γ) and tumor necrosis factor-beta. Immune cells also express Fas ligand which cause cell death in infected hepatocytes[11].

Animal models have enabled the precise description of the kinetics of viremia throughout infection. In particular, chimpanzee models have revealed that HCV RNA levels increase rapidly upon initial infection[12]. Thereafter, a slow decrease in viremia is observed. It is accepted that the innate immune response in hepatocytes contributes to the second phase of slowed viral replication[13]. This response includes type I interferon responses and the antiviral activity of plasmacytoid dendritic cells and NK cells. Thus, an ineffective innate immune response can result in disease progression.

The adaptive immune response to HCV is mediated by the humoral and cellular immune systems. HCV-specific T lymphocytes are detectable five to nine weeks after infection[14,15], which coincides with the onset of hepatitis. Both $CD4^+$ and $CD8^+$ T cells have been shown to play major roles in the outcome of HCV infection. $CD8^+$ T cells inhibit HCV replication by cytolytic and non-cytolytic effector mechanisms[16] that are highly dependent on $CD4^+$ T cell activation. $CD4^+$ T cells are critical for the elimination of viruses through tightly regulated mechanisms. $CD4^+$ T-helper cells are divided into four subsets (Th1, Th2, T regulatory, Th17) based on their expression profile of transcription factors and secreted cytokines. An effective Th1 cellular function is crucial for an adequate immune response against HCV, given the specific production of IFN-γ by this cellular subtype. Unbalanced Th1/Th2 T-cell responses in the liver are a characteristic of hepatic inflammation and subsequent liver fibrosis as a result of HCV infection[17]. Clinical data reveals increased interleukin-17 levels in HCV-infected patients who had increased alanine transaminase (ALT) values, suggesting that Th17 cells in chronic hepatitis C infection might be associated with control of liver injury. However, these observations are preliminary and not fully conclusive[18,19]. Indeed, vigorous peripheral and intrahepatic virus-specific T cell responses that target multiple epitopes have been described in patients who recover from HCV infection[13], while a weak and functionally impaired T cell response has been reported in patients who fail to clear the virus. Consistent with these findings, the role of T regulatory cells in HCV seems to range from suppressing T-cell responses directed against HCV to down-regulating the immune responses causing liver damage[20]. In addition, animal models have

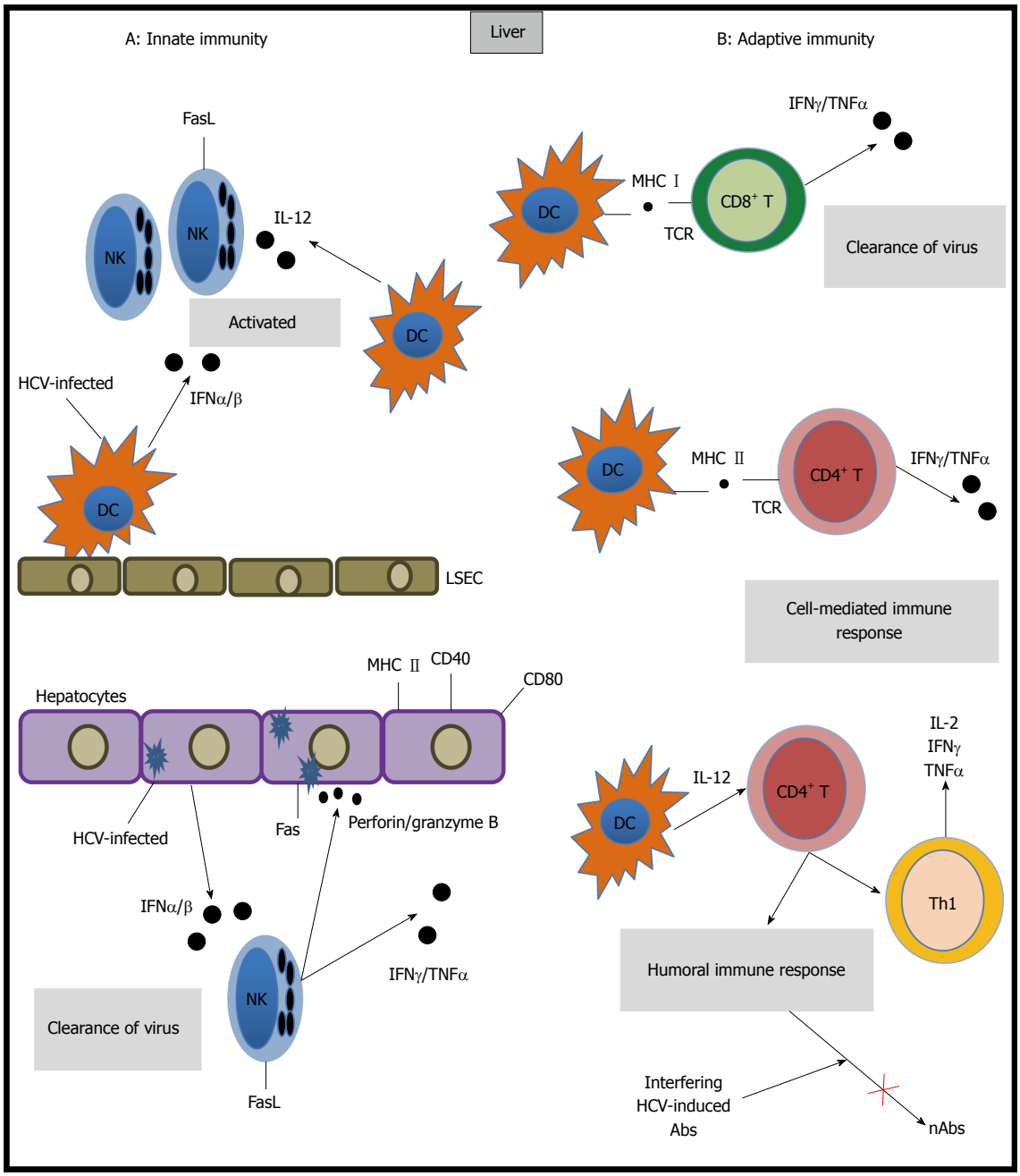

Figure 1 Mechanisms of Immune response to hepatitis C virus. Multiple innate (A) and adaptive immune (B) components are involved in hepatitis C virus (HCV) infection (see text), dendritic cells (DC), natural killer (NK) cells, $CD4^+$, $CD8^+$ T cells and B-cell mediated humoral immune response are crucial for disease outcome. IFN-γ: interferon-gamma; TNF-α: tumor necrosis factor-α; IL: Interleukin; nAbs: Neutralizing anti-HCV antibodies.

indicated that early expression of memory precursor markers on HCV-specific T cells or the expression of ligands for these memory markers in the liver predicts the outcome of acute infection[17] (Figure 1).

Neutralizing antibodies

The generation of neutralizing antibodies represents a protective strategy in host immunity. Neutralizing anti-HCV antibodies (nAbs) were originally described in chimpanzees. These antibodies target epitopes within the hypervariable region 1 (HVR1) of envelope glycoprotein E2[21]. In humans, nAbs were identified in a cohort study of transplant recipients in which the incidence of HCV viremia was lower in patients receiving immunotherapy (anti-HBV immunoglobulins contaminated with anti-HCV immunoglobulins) compared to patients whose therapy did not include anti-HCV antibodies[22], indicating the potential contribution of neutralizing antibodies to viral control. Functional analysis and neutralization experiments using sera from chronically HCV-infected patients have demonstrated that host neutralizing responses target viral entry at a step after initial HCV binding. Initial HCV attachment to the cell surface is likely facilitated by interactions with attachment factors that include the

LDL receptor[5]. Upon initial attachment, at least six host entry factors including scavenger SRB- I , CD81, the tight junction proteins claudin 1 and occludin[23], receptor tyrosine kinases[24] and the Niemann-Pick C1-like 1 cholesterol absorption receptor[25] are important for particle internalization. Indeed, several E2 domains have been shown to play pivotal roles in viral entry and neutralization. Two regions in the E2 viral envelope glycoprotein have increased genetic variability within quasispecies and among genotypes and have been identified as hypervariable regions. Antibodies that demonstrate broadly neutralizing activity tend to be directed against conserved and conformational epitopes within E2, which inhibit the interaction between CD81 and E2[26-30].

Mechanisms of immune evasion by HCV

The strategies of HCV persistence and evasion of the immune response involve multiple mechanisms. The high genetic variability of HCV is a major contributor to the development of chronic HCV infection. It has been shown that HCV constantly circulates in the patient and rapidly evolves into genetically distinct but closely related variants within quasispecies. The simultaneous presence of different variants has been postulated to allow for the rapid selection of mutants that are best adapted to changes in the host environment. Genetic analysis reveals a positive correlation between distinct HCV quasispecies, viral clearance and a slowly adapting viral population, whereas distinct patterns of progression to chronicity are related to selective pressure on the HVR1 region of HCV E2. Moreover, chronic progression is associated with the rapid evolution of quasispecies[31], and single point mutations that result in glycosylation site modifications during viral genetic and conformational changes have been suggested to be responsible for masking the envelope glycoprotein binding sites[32-36]. The result is viral persistence in the body despite the presence of an immune response.

During the innate immune response, HCV interferes with innate signaling pathways using its structural and non-structural proteins to interact with factors that regulate ISGs, thus attenuating innate responses[37-39]. In addition, patients who fail to clear the virus show a weak and functionally impaired T cell response. This result strongly suggests that HCV also employs strategies to escape host adaptive immunity.

The action of nAbs may be blocked by the presence of interfering HCV-induced Abs[32,40,41]. There are two proposed mechanisms through which lipoproteins may provide HCV with protection from nAbs: masking viral epitopes by associating with LDL and very-low density lipoprotein (VLDL) or accelerating viral entry by interactions with high-density lipoprotein (HDL). In both cases, HCV lipoprotein-dependent protection results in limiting the exposure of viral epitopes to nAbs[42]. Recently, it has been suggested that in HCV genotype 2a, the viruses that combine with LDL and VLDL and are consequently distributed in low-density fractions are more capable of escaping neutralizing antibodies compared to viruses distributed in high-density fractions[43]. In addition, HCV is able to infect B-lymphocytes and induce hypermutations in the heavy chains of immunoglobulins. These hypermutations may decrease the affinity and specificity of anti-HCV antibodies and may allow the virus to escape from the immune system[44]. HCV dissemination by cell-to-cell transmission may also contribute to viral persistence by avoiding surveillance of nAbs present in the serum[45] (Figure 1).

HCV VIRUS AND LIPID METABOLISM

HCV entry

After its discovery, HCV was found to be associated with lipoproteins. Thomssen *et al*[46] demonstrated the existence of distinct HCV particles categorized as high and low density particles. These particles, also recognized as lipo viro particles (LVP), are rich in triglycerides (TG) and can be almost completely precipitated by anti-Apo lipoprotein B and E. LVPs contain HCV RNA and structural viral proteins, mainly E1 and E2 that attach the virus to the hepatocyte surface through specific receptors[6,47].

Attachment and internalization of HCV into the cell represent the first steps in the viral replication cycle. The LDL receptor is likely the mediator of viral entry through Apolipoprotein E (ApoE), the major structural agent of infectious LVP and the natural ligand of LDL-R[48]. ApoE exists in three common isoforms (E2, E3 and E4) that affect LDL receptor binding[49]. Allele 4 is associated with clearance of HCV and protection against severe liver damage[50]. Allele 2 is associated with clearance and binds poorly to LDL-R; it is plausible that this defective binding could result in poor uptake of HCV LVP into hepatocytes, thus altering the balance between virus replication and the immune response by decreasing viral replication and favoring clearance. In contrast, allele 3 is associated with persistence[51]. Recently, an association between levels of ApoE and interferon sensitivity was found, and ApoE was shown to induce a higher LDL concentration, potentially inhibiting the binding of HCV to LDL-R. The association between ApoE and the peg-interferon treatment response suggests that lipid modulation is a potential target for modifying interferon sensitivity, favoring the clearance of HCV and avoiding progression to chronic infection[52] (Figure 2).

HCV replication, virion assembly and secretion: Role of apolipoprotein B and microsomal triglyceride transfer protein

HCV RNA replication is strongly influenced by the intracellular levels and composition of fatty acids, including cholesterol. Recent studies have demonstrated that the expression of genes involved in biosynthesis, degradation and intracellular transport of lipids is altered during HCV infection[53,54]. The positive RNA strand of HCV induces remodeling of the intracellular membranes to generate compartments where RNA replication takes place.

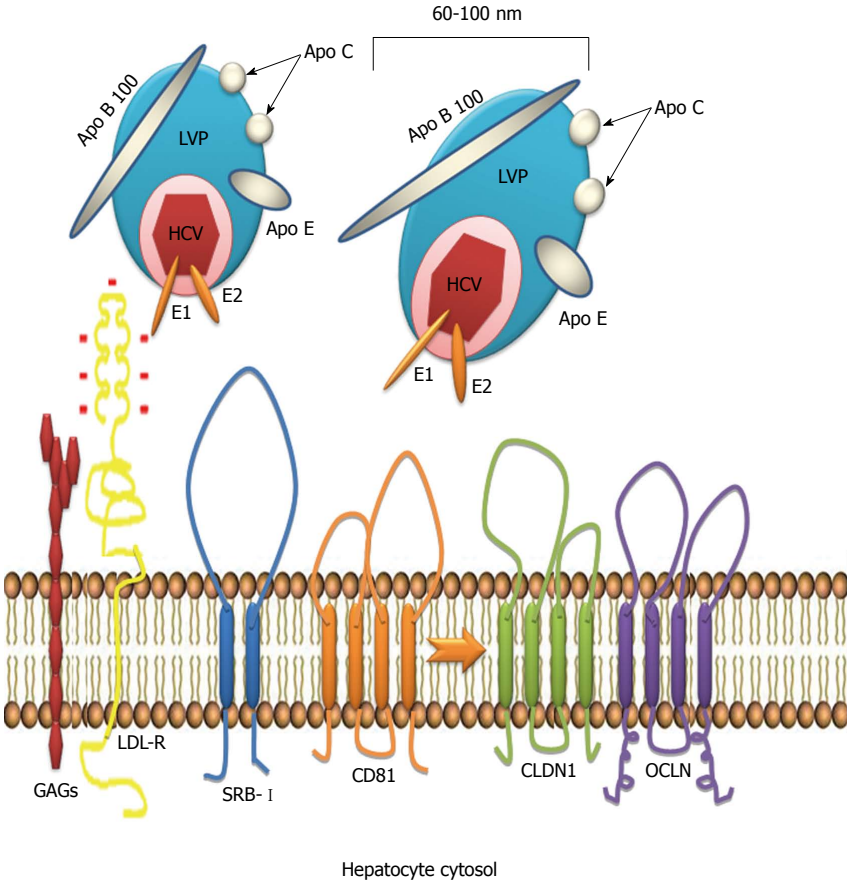

Figure 2 Hepatitis C virus entry. Hepatitis C virus (HCV) binds to lipoproteins and forms the lipo viro particle (LVP). LVP is attached by the hepatic low density lipoprotein (LDL) receptors through viral surface membrane proteins E1 and E2. After the initial phase, the LVP interacts with several input factors: the scavenger receptor class B type Ⅰ (SRB-Ⅰ), the membrane receptor CD81, coreceptors claudin 1 (CLDN1) and ocludin (OCLN). LVP is internalized into the cytosol by endocytosis.

The NS5B viral protein is responsible for generating the membranous web required for RNA replication through diverse mechanisms[55]. Transcription of genes related to lipid metabolism is augmented during HCV infection. Sterol regulatory element-binding protein (SREBP) expression, which controls the transcription of specific genes required for cholesterol biosynthesis, is increased by the NS2 and NS4B HCV proteins. However, the exact mechanism responsible for disruption of host lipid metabolism by HCV infection is not yet clear. Understanding the components involved in this process will allow the possible design of specific therapeutic targets.

Some authors have reported that 30% of the total protein in complexes associated with HCV RNA is functionally involved in lipid metabolism[56]. Many lipids are crucial for the viral lifecycle, and inhibitors of cholesterol/fatty acid biosynthetic pathways inhibit viral replication, maturation and secretion[57]. In humans, apolipoprotein B (ApoB)-100 and ApoB-48 are obligatory proteins for the assembly of hepatic VLDL and intestinal chylomicron, respectively. VLDL assembly occurs *via* a two-step mechanism involving the formation of ApoB-containing VLDL precursor particles in the lumen of the endoplasmic reticulum, a step that requires microsomal triglyceride transfer protein (MTP)[58]. Hepatic VLDL assembly and secretion are also profoundly influenced by alterations in the *de novo* biosynthesis of phospholipids, such as phosphatidylethanolamine and phosphatidylcholine. Increased VLDL-TG concentration is a central feature of diabetic dyslipidemia and is largely caused by increased VLDL-TG secretion[59]. According to clinical data and experimental models, the HCV core protein has been shown to inhibit the MTP protein[60]. This enzyme plays a rate-limiting role in VLDL assembly and ApoB secretion[61].

Inhibition of VLDL assembly and secretion also affects virion morphogenesis and secretion, leading to the notion that HCV may hijack the VLDL secretion pathway for virion maturation and secretion. The reliance of HCV on host lipid metabolic pathways for its replication, morphogenesis and release requires the modulation of host lipid pathways by HCV to create a lipid-rich intracellular environment favorable for replication. HCV assembly and maturation in hepatocytes depend on MTP and ApoB in a manner that parallels the formation of VLDL[56,62]. Inhibitors of MTP and reduction of the expression of ApoB lowers virion production[56,63].

Mechanism of HCV-associated steatosis

Steatosis, or the accumulation of hepatocellular lipid droplets, and altered serum lipid profiles are common consequences of HCV infection. The presence of ste-

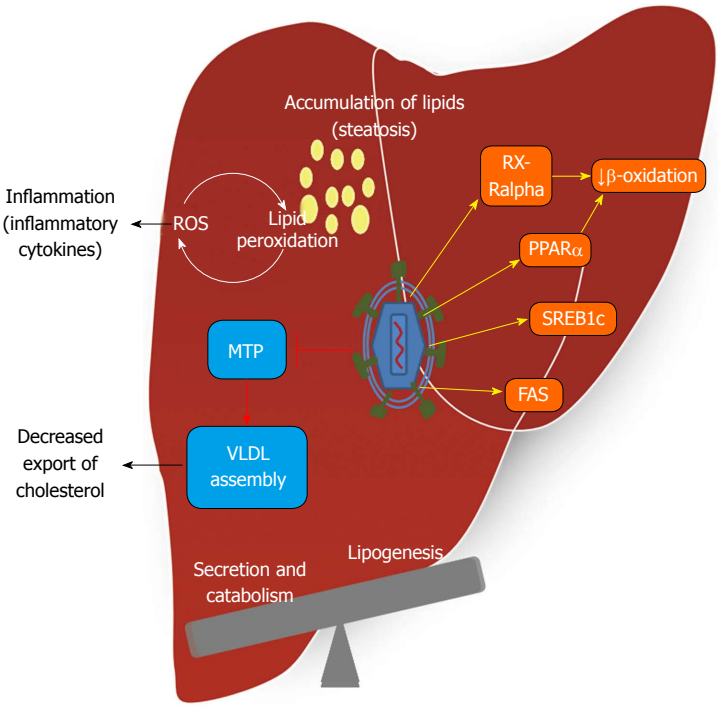

Figure 3 Hepatitis C virus effect in lipid metabolism and development of steatosis. Hepatitis C virus (HCV) alters intracellular lipid metabolism to create an environment rich in lipids to facilitate its replication. This allows the accumulation of lipids, decrement in exportation of very low density lipoprotein (VLDL) and development of steatosis, a pathological phenotype associated with HCV chronic infection. Reactive oxygen species (ROS) generated during infection cause lipid peroxidation triggering inflammation. MTP: Microsomal triacylglycerol transfer protein; RXRα: Retinoid X receptor-alpha; PPARα: Peroxisome proliferators-activated receptor alpha; SREB1c: cholesterol regulatory element binding protein-1c; FAS: Fatty acid synthase.

atosis in infected patients with HCV varies from 30% to 70% depending on ethnic and other factors, such as alcohol consumption, being overweight, obesity and factors that are also risk factors for non-alcoholic steatohepatitis[64]. In patients with chronic HCV, serum cholesterol is significantly reduced when compared to appropriately matched controls. This has been specifically analyzed in HCV genotype 3 infections in specific populations[65], and this metabolic effect can be reversed after successful HCV eradication. However, large-scale studies including samples from distinct populations and different genotypes are necessary to determine the roles of viral genotypes and host genetic factors in this process.

HCV modulates lipid metabolism to create an environment rich in lipids favorable for viral replication. Consistent with this lipid modification, each step of the viral replication cycle appears related to lipid metabolism[66]. The interaction of HCV proteins with hepatic cellular components contributes to the interference with lipid and carbohydrate metabolism, resulting in the release of cytokines, insulin resistance, inflammation, oxidative stress and steatosis[67,68]. The mechanism of triglyceride accumulation induced by HCV infection is multifactorial. de Gottardi *et al*[69] reported that host lipid metabolism may be modulated by HCV at three levels: impaired lipoprotein secretion, enhanced lipogenesis, and impaired fatty acid degradation. These detrimental alterations incurred during HCV infection then manifest as the pathological basis for some HCV-associated diseases, most notably steatosis and metabolic syndromes such as insulin resistance, obesity, and HCC[70-72]. MicroRNAs (miRNAs) exert regulatory control through modulation of many targets. In the liver, miRNA-122 is important for regulating lipid metabolism[73,74] and aberrant expression of miRNAs is linked to HCV infection[75]. It has recently been reported that HCV replication induces the expression of miR-27 *in vitro* and *in vivo*. This results in larger and more abundant lipid droplets and coincides with the repression of regulators of triglyceride homeostasis including peroxisome proliferator-activated receptor alpha (PPARα), identifying HCV's up-regulation of miR-27 as a novel mechanism that may contribute to the development of steatosis[76].

In conjunction, the main lipid alterations in HCV are enhanced lipogenesis, reduced secretion and β-oxidation of lipids regulated by transcription factors, hormones and key enzymes that are briefly described below (Figure 3).

PPARs: PPARs are ligand-dependent transcription factors. The three subtypes of PPARs (PPARalpha, PPARdelta, and PPARgamma) are differentially expressed in tissues, and play pivotal roles in lipid, lipoprotein and glucose homeostasis[77]. PPARalpha, PPARdelta, and PPARgamma are differentially involved in HCV infection. A clear effect of PPARα in HCV RNA replication has been described and a recent report has shown that PPARα-selective antagonists inhibit HCV replication, while PPARα is not involved in this process[78]. PPARα is a transcription factor in the nuclear hormone receptor superfamily; it is involved in the differentiation of normal adipocytes, and its major function is to control fatty acid oxidation and activation. PPARα participates in enhancing the expression of adiponectin messenger RNA (mRNA) and serum adiponectin levels. PPARα deficiency causes defective hepatic fatty acid oxidation[79,80], while persistent activation of PPARα is essential for the pathogenesis of hepatic steatosis and HCC induced by HCV infection[81]. Dharancy *et al*[82] reported that PPARα mRNA expression was significantly reduced in the liver of chronic HCV patients infected with HCV genotype

3 when compared with HCV genotype 1 infections. A better understanding of the role of PPARα and its interaction with HCV proteins may help in developing novel therapies against HCV-induced steatosis and HCC.

Adiponectin and leptin: Adiponectin is an insulin-sensitizing protein that is abundantly expressed in white adipose tissue[83] and is a member of the adipocytokine family. Adiponectin improves hepatic insulin sensitivity, decreases lipid accumulation in macrophages and has anti-inflammatory properties[84-86]. Serum adiponectin levels in humans depend upon metabolic activity; it is present as a low molecular weight trimer and a high molecular weight (HMW) hexamer. HMW adiponectin is the biologically active form[87]. Adiponectin exerts its effect *via* two receptors, the adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). AdipoR1 is expressed in skeletal muscles, and AdipoR2 is expressed in the liver[88]. AdipoR1 is associated with AMP-activated protein kinase (AMPK) activation, while AdipoR2 is associated with PPARα activity. Some insights regarding the pathways of steatohepatitis have been identified by impaired lipid accumulation due to hepatic loss of adiponectin receptors, which play an important role in fatty acid accumulation by up-regulating the expression of enzymes during HCV infection, including AMPK, fatty acid synthase (FAS), acetyl-CoA carboxylase, liver gluconeogenic enzyme and phosphoenolpyruvate-carboxykinase[79,80]. Adiponectin is assumed to protect hepatocytes from triglyceride accumulation by increasing the β-oxidation of free fatty acids or decreasing *de novo* production of free fatty acid in hepatocytes[89]. In contrast to the anti-inflammatory role of adiponectin, leptin is a pro-inflammatory adipocytokine identified as one of the best markers of total body fat; its elevated expression can result in stimulation of cellular lipolysis and fatty oxidation, promoting a negative energy balance. Both adiponectin and leptin are crucial for hepatic steatosis[90]. However, data concerning the roles of adiponectin and leptin on HCV-related steatosis remain divergent. This is mainly due to the multiple functions involving adipocytokines. By using a HCV core-transgenic mouse model, a recent report reveals that HCV core-induced, non-obese hepatic steatosis is associated with down regulation of the *leptin* gene in visceral fat and hypoadiponectinemia[91]. A better understanding of this process may be valuable in the design of new therapeutic interventions, particularly in the cases of non-obese hepatic steatosis involving HCV infection.

AMPK: AMPK is a heterotrimeric protein with serine/threonine protein kinase activity that works as a sensor of cellular energy status and enables metabolic adaptation to the environment, such as in nutritional stress[92-94]. AMPK plays a key role in the regulation of both lipid and glucose metabolism. Activated AMPK inhibits energy-consuming biosynthetic pathways such as lipogenesis and activates ATP-producing catabolic pathways such as β-oxidation. A study demonstrated that phosphorylation of AMPK at threonine 172 causes dramatically reduced AMPK activity in cells infected with HCV or harboring an HCV subgenomic replicon. Thus, inhibition of AMPK is required for HCV replication and restoration of AMPK activity may represent a target for anti-HCV therapies[95,96]. The anti-HCV activity of 2-octynoic acid (2-OA), a compound used in perfumes, lipstick, and many food flavorings, has recently been revealed *in vitro*. This activity seems to be associated with the activation of AMPK by 2-OA, which regulates ISGs and suppresses miRNA-122 expression, inhibiting HCV infection. This represents a novel mechanism to explain inhibition of infection by AMPK[97].

SREBP: SREBP plays an important role in the regulation of lipid synthesis and cholesterol metabolism. The *SREBP* gene encodes three isoforms (SREBP-1a, SREBP-1c and SREBP-2[98] that regulate genes involved in cholesterol synthesis. SERBP-1a is an activator of cholesterol and fatty acid synthesis, while SERBP-1c regulates genes involved in lipid synthesis[99-102]. SREBP-1c activates the lipogenesis pathway in response to insulin. HCV infection and the HCV core protein up-regulate the expression of SREBP-1c and cause the development of fatty liver[103]. In non-alcoholic fatty liver disease, SERBP-1c is expressed at a level up to five-fold higher than observed in controls[104].

It has been demonstrated that HCV infection enhances the proteolytic cleavage of SREBP precursors in hepatic cells. The HCV NS2 and NS4B proteins can up-regulate SERBP-1c and consequently promote enhanced transcriptional activity of fatty acid synthase[105,106].

Animal models have been used to investigate the effect of the HCV core and NS proteins on *SREBP* gene regulation, and these models have indicated that HCV proteins that interfere with SREBP lead to steatosis[105,106]. The host subtilisin/kexin/isozyme/1 (SKI-1) or site 1 (S1P) plays a crucial role in the proteolytic activation of SREBP. The use of a SKI-1/S1P-specific protein-based inhibitor recently demonstrated that SKI-1/S1P inhibition blocks HCV infection in hepatoma cells by a mechanism that is associated with dramatic reduction in the number of lipid droplets and adipose differentiation-related protein/perilipin 2. The inhibition of virus assembly from infected cells identifies SKI-1/S1P as both a regulator of the HCV lifecycle and a potential host-directed therapeutic target against HCV infection[107].

Retinoid X receptor alpha: The retinoid X receptor (RXR) family is a family of nuclear receptors that target and regulate multiple signaling pathways. RXRs control gene expression by binding cooperatively as a dimer to hormone responsive elements[108,109]. RXRs form homodimers and are involved in 9-*cis* retinoic acid-mediated gene activation. RXRs exist as three isoforms, namely RXRα, RXRβ and RXRγ; the RXRα isoform is abundantly expressed in the liver and regulates cell proliferation and differentiation.

Table 1 Genes and hepatitis C infection

Lipid metabolism genes altered by HCV		
Gene	Protein	Effect
SREBP	Sterol regulatory element-binding protein	Core protein increases the gene expression[110]
PPARα	Peroxisome proliferators-activated receptor alpha	HCV infection led to reduction in gene expression[126]
MTP	Microsomal triacylglycerol transfer protein	Core protein led to reduction in MTP activity and lower gene expression[127,128]
PEPCK	Phosphoenolpyruvate carboxykinase	NS5A increases gene expression and development of steatosis[129]
FAS	Fatty acid synthase	Core protein induces FAS promoter activity and severity of steatosis[115]
RXRα	Retinoid X receptor-alpha	Core protein enhances the transcriptional activity and contributes to the pathogenesis of infection[112]
APOE	Apolipoprotein E	HCV forms lipoviroparticles and hijacks ApoE for entry into hepatocyte[48]
Genes associated with spontaneous clearance of HCV		
Gene	Protein	Allele
IL28B	Interleukin 28B	rs12979860 CC[130]
IL28B	Interleukin 28B	rs8099917 TT[131]
IL28B	Interleukin 28B	ss469415590DG[132]
KIR	Natural killer cell immunoglobulin-like receptor	KIR3DS1[133]
TNFα	Tumor necrosis factor-α	-863CC[134]
APOB	Apolipoprotein B	rs934197 TT[135]

MTP: Microsomal triacylglycerol transfer protein; FAS: Fatty acid synthase; HCV: Hepatitis C virus; SREBP: Sterol regulatory element-binding protein; PPARα: Peroxisome proliferator-activated receptor alpha; RXRα: Retinoid X receptor alpha.

Some reports have suggested an interaction between HCV core proteins with RXRα and shown that the HCV core protein binds to the DNA-binding domain of RXRα, leading to an increase in binding of RXRα to its DNA response element[110,111]. In addition, RXRα is activated in cells expressing the HCV core protein and in the livers of HCV core-transgenic mice that develop hepatic steatosis and HCC. The HCV core protein may compete with p50- and p65-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) subunits for direct interaction with RXRα. This competition may influence signaling *via* NF-κB, a regulator of many cellular functions and lipid synthesis, and up-regulate the enzymes acyl CoA oxidase and retinol binding protein Ⅱ, exacerbating steatosis by increasing oxidative stress and decreasing β-oxidation[111,112]. These reports indicate that modulation of RXRα controls gene expression by interacting with the core protein and contributes to pathogenesis of HCV infection[112].

FAS: FAS is a protein that is directly linked to intracellular lipid synthesis and plays a central role in triglyceride accumulation in the liver. FAS catalyzes the conversion of acetyl CoA and malonyl CoA to saturated fatty acids, which are then converted to TG after etherification[106,113]. Yang *et al*[114] have demonstrated that HCV infection directly induces FAS expression, while Jackel-Cram *et al*[115] have reported that HCV-3a is a stronger teratogenic factor than HCV-1b. These authors reported that a single amino acid substitution at position 164 (phenylalanine) of the HCV-3a core protein can up-regulate FAS activity. Therefore, the short sequence YATG in HCV-1b and FATG in HCV-3a is responsible for FAS up-regulation at the transcriptional level[114]. However, further studies are required to understand the molecular mechanism of FAS activation.

GENETICS AND HCV INFECTION

Recent progress in the field of molecular genetics has revealed that the clinical outcome and response to treatment for HCV may be predetermined by genetic polymorphisms. Genes related to lipids, metabolism and the immune response have been studied (Table 1). Large-scale genetic epidemiological studies are required to attain adequate statistical power. Identifying the relationship between specific genes and the progression of HCV infection is a crucial step toward understanding the pathogenesis of infection.

DYSLIPIDEMIAS AND HCV INFECTION

The lipid profile in chronic HCV-infected patients presents low levels of total cholesterol, HDL and LDL regarding non-infected individuals. In addition, these levels are significantly lower in patients who present with fatty liver. HCV-genotype 3-infected patients show a higher incidence of fatty liver development. The relationship of these lipid alterations with HCV infection is important for the lifecycle of the virus, and it is positively correlated with the response to antiviral treatment, especially in the setting of genotype 3 infections[57].

Studies have demonstrated the presence of hypobetalipoproteinemia in patients infected with HCV[116]. The pathogenesis of hypobetalipoproteinemia in HCV patients is unclear. Recently, hepatic steatosis has been correlated with this type of dyslipidemia. However, the influence of viral infection on these parameters has not been thoroughly investigated. It has been demonstrated that hepatic fibrosis is increased as serum levels of ApoB decrease. Thus, there is a strong negative correlation between fibrosis and ApoB levels[117].

Studies report that serum triglyceride levels are decreased in patients with HCV; however, in these studies, more than 50% of patients had liver cirrhosis and HCC[118]. Thus, the decrease in TG cannot be attributed to the presence of virus alone. In more recent studies, where HCV patients without cirrhosis or HCC were analyzed, the prevalence of TG was similar to control patients without HCV. However, TGs in the fasting state, transported

only by VLDL, are found at significantly lower levels in HCV-infected patients compared to individuals without HCV infection. The levels of TGs in different stages of fibrosis in patients with HCV have been compared and no differences were found. Differences were only found in patients with cirrhosis. In contrast, the levels of TGs transported by VLDL declined with progression of liver damage until cirrhosis was reached. These data indicate that hypertriglyceridemia in HCV patients is not of viral origin. In contrast, the decreased serum levels of TG can be explained by the interference in maturation and excretion of VLDL caused by the viral lifecycle[119].

Dyslipidemias in Mexico

Chronic diseases associated with diet and lifestyles, including obesity and dyslipidemias, have genetic components. Currently, Mexico and the United States are experiencing the largest obesity epidemic in the world. The significant increase in prevalence of these diseases in recent years strongly suggests the influence of environmental factors in their development. High levels of cholesterol and lipid disorders are important risk factors for developing diseases including hepatic and cardiovascular diseases. Pathologies associated with high levels of cholesterol represent one of the eight main risk factors for mortality in Mexico[8,120]. Hypercholesterolemia has been described as a public health problem in Mexico since 1988 when the Secretariat of Health conducted the first national survey related to serum cholesterol levels among the Mexican population. In 1993, a new study was performed (National Survey of Chronic Diseases) revealing that the prevalence of hypercholesterolemia had risen to 35.5%, a 10% increase compared to the previous study. This trend continued during the coming years, resulting in an increase in prevalence of hypercholesterolemia from 35.3% to 42.6%[121]. Additionally, serum TGs are higher and HDL is lower among Mexicans when compared to other populations worldwide. In 2000, data from the Secretariat of Health revealed that fasting serum samples from 2351 adults had a mean total cholesterol of 197.5 mg/dL, HDL cholesterol of 38.4 mg/dL and TGs of 181.7 mg/dL. Only 6.1% of the study population was diagnosed with dyslipidemia and 85.88% did not know that they were ill[121]. Detailed analysis of the data revealed that the most frequent dyslipidemia was hypobetalipoproteinemia (low HDL), followed by hypertriglyceridemia and hypercholesterolemia. The most common combinations were high levels of TGs and low HDL cholesterol, and high levels of TGs with high total cholesterol (mixed dyslipidemia).

It is currently accepted that there is an important association between being overweight, obesity and various types of dyslipidemia[121]. As in the United States, the obesity epidemic in Mexico has dramatically increased in children and adults. In 2000, the Secretariat of Health in Mexico revealed an association between obesity and hypertriglyceridemia. Obese adults compared with individuals of normal weight were four times more at risk for a diagnosis of high cholesterol, low cholesterol HDL, high TGs or any combination of these conditions[121]. Currently, even children have been detected with high blood levels of cholesterol and triglycerides, most likely due to the marketing of processed foods with high sugar or fat content, changes in dietary patterns and the abuse of food rich in animal fat. It has been described that 100 mg of dietary cholesterol for each 1000 kcal results in 12 mg/dL increase in the concentration of blood cholesterol, and that children and adolescents with high levels of cholesterol are more likely to continue having high levels into adult stage[122].

Mexico has been reported to be a low endemic area for HCV[123,124]. Moreover, a low association between HCV infection and HCC has been reported in the country[125]. Given that lipid components associated with HCV infection are finely modulated in the Mexican population, it is plausible to hypothesize that the progression of infection may be regulated by the characteristics of this population's lipid composition.

FINAL REMARKS

Ineffective viral escape from the immune response and effective T cell activity, together with the absence of interfering HCV-induced Abs, are factors that may contribute in combination to the spontaneous clearance of HCV. In contrast, exhausted T cell responses resulting in impaired T cell activity and viral adaptation to the host immune response may result in chronicity. In addition to the recognized role of lipoproteins during the initial steps of HCV infection, lipoproteins can also provide HCV with protection from nAbs, either by masking viral epitopes by associating with LDL and VLDL or by accelerating viral entry *via* HDL and thus limiting the exposure of viral epitopes to nAbs. ApoE alleles 2 and 4 are associated with HCV clearance and protection against severe liver damage. Furthermore, association between ApoE levels and IFN sensitivity suggest that lipid modulation is a potential target for preventing HCV disease progression.

When comparing serum lipid concentrations with those of other populations of the world, it is notable that Mexicans have higher concentrations of TGs and lower HDL cholesterol. Hypercholesterolemia is among the eight most important risk factors for mortality in the country. Moreover, in Mexico, as in the United States and other developed countries, obesity has significantly increased in recent years. Analysis of the 2000 Mexican National Health Survey significantly associated obesity with hypertriglyceridemia, followed by hypercholesterolemia. This reveals a unique lipid profile in the Mexican population that, in conjunction with genetics and lifestyle, might be responsible for the immune response during chronic diseases, including HCV infection.

CONCLUSION

Advances in understanding HCV disease outcome suggest that individualized therapies that account for fac-

tors, such as lipid modulation, lifestyle and genetics, in conjunction with immune-based therapies are required to establish better strategies for controlling infection with HCV.

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