World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i10.1337

World J Hepatol 2015 June 8; 7(10): 1337-1346
ISSN 1948-5182 (online)

REVIEW

Liver steatosis in hepatitis C patients

Emilio González-Reimers, Geraldine Quintero-Platt, Melchor Rodríguez-Gaspar, Remedios Alemán-Valls, Onán Pérez-Hernández, Francisco Santolaria-Fernández

Emilio González-Reimers, Geraldine Quintero-Platt, Melchor Rodríguez-Gaspar, Remedios Alemán-Valls, Onán Pérez-Hernández, Francisco Santolaria-Fernández, Servicio de Medicina Interna, Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, 38320 Canary Islands, Spain

Author contributions: González-Reimers E, Quintero-Platt G, Rodríguez-Gaspar M, Alemán-Valls R, Pérez-Hernández O and Santolaria-Fernández F contributed to the review of the literature; González-Reimers E and Quintero-Platt G contributed to the drafting of the manuscript.

Conflict-of-interest: The authors declare that there is no conflict of interest regarding this manuscript.

Correspondence to: Dr. Emilio González-Reimers, Servicio de Medicina Interna, Hospital Universitario de Canarias, Universidad de La Laguna, Ofra s/n, Tenerife, 38320 Canary Islands, Spain. egonrey@ull.es
Telephone: +34-922-678600

Received: July 31, 2014
Peer-review started: August 1, 2014
First decision: September 16, 2014
Revised: February 8, 2015
Accepted: March 5, 2015
Article in press: March 9, 2015
Published online: June 8, 2015

Abstract

There is controversy regarding some aspects of hepatitis C virus (HCV) infection-associated liver steatosis, and their relationship with body fat stores. It has classically been found that HCV, especially genotype 3, exerts direct metabolic effects which lead to liver steatosis. This supports the existence of a so called viral steatosis and a metabolic steatosis, which would affect HCV patients who are also obese or diabetics. In fact, several genotypes exert metabolic effects which overlap with some of those observed in the metabolic syndrome. In this review we will analyse the pathogenic pathways involved in the development of steatosis in HCV patients. Several cytokines and adipokines also become activated and are involved in "pure" steatosic effects, in addition to inflammation. They are probably responsible for the evolution of simple steatosis to steatohepatitis, making it difficult to explain why such alterations only affect a proportion of steatosic patients.

Key words: Hepatitis C virus steatosis adiponectin; Leptin; Insulin resistance; Proinflammatory cytokines; Triglyceride synthesis; Fatty acid oxidation

Core tip: Chronic hepatitis C virus (HCV) infection can lead to steatosis and steatohepatitis. Increased liver triglyceride synthesis is mediated by several transcription factors such as sterol regulatory element-binding protein (SREBP) whose expression is enhanced, in turn, by HCV core protein. Chronic HCV infection is also associated with insulin resistance that seems to be selective because although it activates systemic lipolysis, it increases triglyceride synthesis within the liver. This is due to the stimulatory effect of insulin on SREBP. It remains to be answered why not all patients with HCV infection and steatosis develop steatohepatitis despite early cytokine activation and metabolic derangements.

González-Reimers E, Quintero-Platt G, Rodríguez-Gaspar M, Alemán-Valls R, Pérez-Hernández O, Santolaria-Fernández F. Liver steatosis in hepatitis C patients. *World J Hepatol* 2015; 7(10): 1337-1346 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i10/1337.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i10.1337

INTRODUCTION

Non-alcoholic steatohepatitis is an increasingly common situation, in which fat-laden hepatocytes trigger an inflammatory response which may evolve to liver cirrhosis[1] and hepatocarcinoma[2]. Diabetes and obesity are the most important causes, since insulin deficiency and/or resistance alter the mobilization of fatty acids from adipose tissue to liver, the oxidative pathways, and lipid trafficking between liver and peripheral tissues. Steatosis and steatohepatitis are also observed in chronic hepatitis C virus (HCV) infection. Although HCV by itself-especially genotype 3a- may lead to liver steatosis, obesity and concomitant alcohol abuse are main factors involved[3]. The "two hit theory" sustains that cytokine activation and increased lipid peroxidation contribute to the evolution of liver steatosis to more advanced stages of steatohepatitis[4]. Throughout this manuscript we will show that cytokine activation may already exist, at least theoretically, in early stages of the disease (simple steatosis), but not all the patients showing simple steatosis develop steatohepatitis.

The outstanding role played by some genotype specific HCV viral proteins, which either have a direct steatogenic effect or induce insulin resistance, explains why some HCV infected individuals show liver steatosis in the absence of obesity and has led to the concept that there are two main pathogenetic mechanisms of steatosis in these patients: the so-called "metabolic" steatosis and "viral" steatosis. In the present paper we will revise the main pathways leading to steatosis in these HCV patients. However, viral and non-viral dependent pathways are intermingled, so we will not treat them separately. Also, although the objective of this review is only to revise mechanisms leading to steatosis, and not steatohepatitis, many pathways involved in simple steatosis are already able to trigger inflammation, which is the hallmark of steatohepatitis, so a precise limit between both clinicopathological stages is lacking. We will comment only those aspects of proinflammatory cytokines involved in the pathogenesis of "pure" steatosis.

As mentioned above, patients infected by genotype 3a HCV develop liver steatosis even in the absence of obesity[5], a finding which supports a direct cytopathic and steatogenic effect of this precise genotype[6]. Recent research has shown that this viral effect depends on several mechanisms which will be commented in this review. HCV genotype 3a up-regulates the expression of fatty acid synthase[7]. There are also data which suggest that in chronic hepatitis secondary to HCV there is decreased mitochondrial β-oxidation, possibly due to mitochondrial damage[8]. In addition, HCV impairs export of very low density lipoprotein (VLDL) particles from the liver to peripheral tissues, by several mechanisms. Hepatocyte release of HCV particles utilises the same pathway used in VLDL export, and HCV mediates inhibition of the microsomal triglyceride transfer protein (MTP), a molecule involved in export of intrahepatocytary triglycerides[9].

In addition, several viral proteins of diverse genotypes interfere with insulin signalling, leading to insulin resistance. Insulin resistance is the hallmark of obesity, but in HCV infection, patients do not necessarily have to be overweight for them to develop insulin resistance: despite the principal role of obesity and associated insulin resistance on liver steatosis, this lesion may develop in the face of a normal body mass index (BMI). Therefore, at any given load of fatty acids, HCV infected hepatocytes up-regulate synthesis of more fatty acids, impair β-oxidation of the available fatty acids, and impede the export of triglycerides (Figure 1).

Increased triglyceride synthesis

Fat mobilization is a necessary condition to develop liver steatosis, and liver steatosis is more intense the greater the BMI[10], also in HCV patients (Figure 2). During fasting-a situation characterized by low insulin levels-, fatty acids are released by the adipocyte and reach the liver, where they are taken up by liver cells and are destined to be used either as fuel, as a source of ketone bodies or they can be combined again with glycerol to be re-esterified as triglycerides. Triglycerides coupled with apoproteins and cholesterol form the so called VLDL which are then exported to peripheral tissues.

A situation with some features similar to those observed during fasting may take place in conditions accompanied by insulin resistance: in adipose tissue insulin fails to suppress lipolysis, so that an increased amount of free fatty acids reaches the liver. But in fasting, insulin levels are low, whereas in situations of insulin resistance, insulin levels are usually high. High insulin levels, even in a situation of insulin resistance and not-supressed lipolysis, still enhance liver triglyceride synthesis, but not adipocyte synthesis of triglyceride. Liver triglyceride synthesis implies esterification of glycerol with fatty acids. These fatty acids may derive from adipose tissue, from ingested fat, and also from ingested carbohydrates, the latter constituting the amount synthesized "*de novo*" by the liver. In insulin-resistant patients with non-alcoholic fatty liver disease the rate of *de novo* lipid synthesis is increased. Donnelly *et al*[11] showed that 26% of the triglycerides stored in the liver of 9 obese subjects with non-alcoholic fatty liver disease derived from *de novo* lipogenesis, in contrast with the 5% contribution (in the fasted state) observed among normal individuals[12]. This increased *de novo* liver lipogenesis in insulin-resistance situations is accompanied by a reduced triglyceride synthesis within the adipocyte, due to decreased availability of glycerol 3 phosphate, which is in turn due to an insulin-resistance-mediated decrease in glucose uptake[13].

Several transcription factors are involved in increased liver lipid synthesis[14]. These are:

(1) Sterol regulatory element-binding proteins (SREBP), especially the SREBP-1c. SREBP-1c enhances transcription of genes required for fatty acid synthesis and predominates in the liver[15]. When cells become

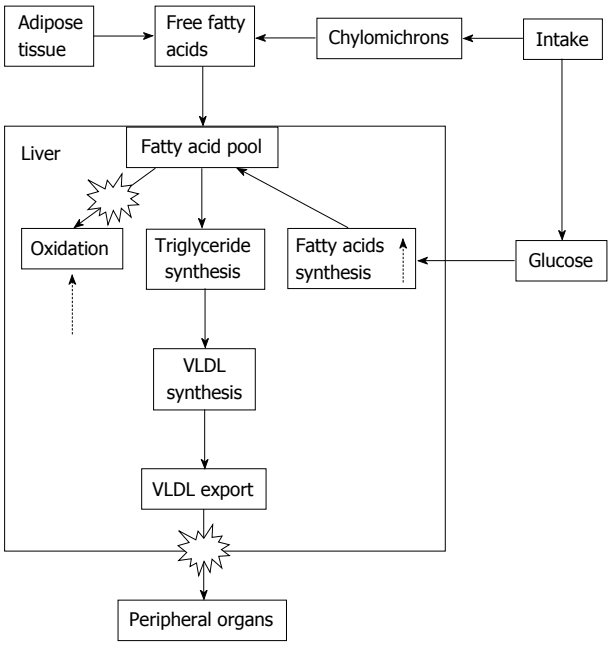

Figure 1 Simplified schematic pathway of lipid metabolism. The symbol corresponds to the points at which hepatitis C virus (HCV) blocks lipid metabolism, and the dotted arrows the point at which HCV enhances it. VLDL: Very low density lipoprotein.

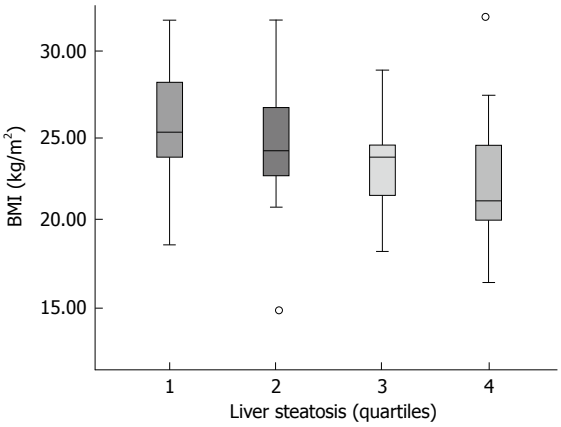

Figure 2 Preliminary data on 83 patients with hepatitis C virus infection. Liver steatosis was histomorphometrically assessed. In this figure, it is shown that the amount of liver steatosis (in quartiles) is related to body mass index.

depleted in cholesterol, a protein called SREBP cleavage-activating protein (SCAP) binds to SREBP and transports it from the endoplasmic reticulum to the Golgi apparatus. In the Golgi apparatus there are two proteases (site 1 protease or S1P, and site 2 protease or S2P) which act sequentially to release the N-terminal active form of SREBP, which enters the nucleus and binds to a sterol responsive element in the enhancer/promoter region of the target genes (for instance, fatty acid synthase), activating transcription. The movement of the SREBP-SCAP complex from the endoplasmic reticulum to the Golgi apparatus is supressed by high intracellular cholesterol levels; therefore, the SRBEP-SCAP system can be viewed as a sensor of

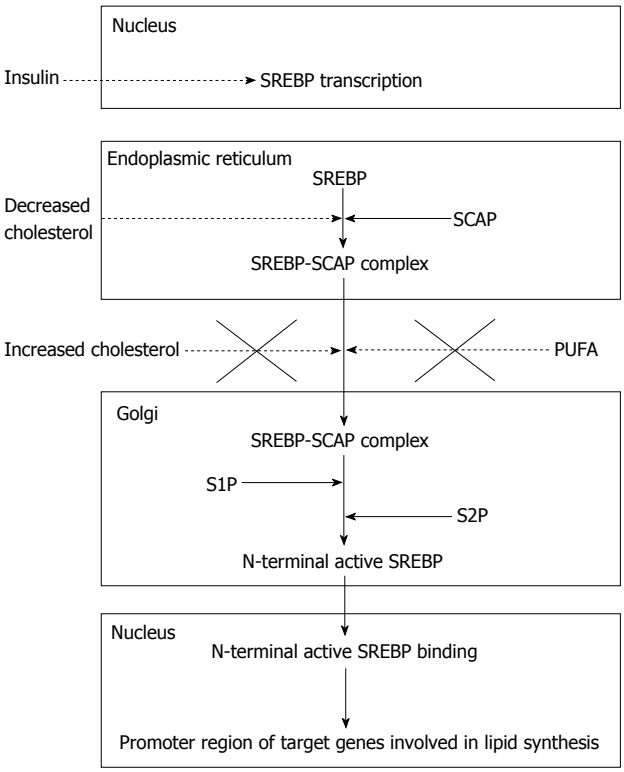

Figure 3 Simplified representation of the effect of steroid response element binding protein on lipid synthesis. Insulin promotes transcription of steroid response element binding protein (SREBP). In the endoplasmic reticulum, SREBP binds to SREBP cleavage-activating protein, a complex which moves to the Golgi apparatus, where the active N-terminal form of SREBP is formed by the sequential action of two proteases (S1P and S2P), and is finally translocated to the nucleus. SCAP: SREBP cleavage-activating protein; PUFA: Polyunsaturated fatty acid.

cholesterol levels in the hepatocyte[16], although this inhibitory action affects SREBP-2. Inhibition of SREBP-1 processing requires the presence of polyunsaturated fatty acids in addition to cholesterol[17] (Figure 3).

SREBP-2 is also present in liver and other organs, and is more specifically involved in cholesterol synthesis. However, when expressed at higher than normal levels, each of the three SREBP isoforms can activate both cholesterol and fatty acid synthesis[18].

SREBP-1a is expressed only at low levels in liver, but in studies performed on genetically engineered mice, overexpression of SRBEP 1a led to a 26-fold increase in fatty liver synthesis and a massive liver steatosis[19].

SREBP transcription is strongly stimulated by insulin[20], whereas glucagon exerts an inhibitory effect. Over-expression of SREBP-1c may lead to an excessive synthesis of fatty acids (and cholesterol and triglycerides) within the liver cell, ultimately leading to liver steatosis[14,21]. Liver X-activated receptors (LXR) α and β are involved in SREBP-1c transcription. These are nuclear receptors that heterodimerize with retinoid X receptors after binding to a ligand. In the case of SREBP, they bind to a LXR response element in the promoter region of the *SREBP-1* gene and activate SRBP-1c transcription[22]. Thus, glucagon, insulin, and

LXR are classical modulators of SREBP-1c transcription.

The activity of SREBP-1c is increased in several situations in which liver steatosis ensues, such as alcoholism (acetaldehyde enhances its transcription[23]), high tumor necrosis factor alpha (TNF-α) levels[24], or HCV infection[25]. HCV core protein enhances both gene expression of SRBP and transcriptional activity of this molecule[26].

On the other hand, SRBP-1 is inactivated by sirtuin-1 (SIRT-1), a molecule whose activity is modulated by several variables, including ethanol and HCV core protein, among others[27]. Sirtuins are involved in the modulation of transcription factor activity by deacetylation of proteins. Biological activity of sirtuins depends on nicotinamide adenine dinucleotide (NAD) availability[28]. Specifically, sirtuin1 deacetylates and inhibitis SREBP-1c activity, therefore decreasing fat synthesis. Ethanol inhibitis sirtuin-1 activity, therefore increasing the lipogenic effect of SREBP 1-c[26]. HCV exerts a similar effect[29].

Sirtuin activity is coupled to that of AMP-activated kinase (AMPK), an enzyme that phosphorylates and, thus, inhibits, acetyl-CoA carboxylase, interrupting the formation of malonyl-CoA, a key step for fatty acids synthesis, and preserving cellular content in NAD[30]. Sirtuin activates AMPK acting on serine/threonine kinase 11, also known as liver kinase B1, a process which leads to an increase in cellular NAD availability, which favours SIRT-1 activity[31]. This reciprocally regulated circuit leads to inhibition of SREBP activity and fatty acids synthesis. It is important to keep in mind that ethanol metabolism consumes NAD, theoretically opposing to sirtuin activation.

Endocannabinoids are also involved in enhanced expression of SREBP-1c[32]. Cannabinoid agonists are orexigenic, and animal models support a role of endocannabinoids on diet-induced liver steatosis[33]. Daily cannabis consumption aggravates steatosis in HCV patients[34]. Conversely, HCV infection may up-regulate cannabinoid receptor 1 expression[35].

(2) However, although cholesterol synthesis seems to depend almost entirely on SREBP activity, suppression of the SREBPs machinery reduces fatty acid synthesis by only 30%[36]. Another transcription factor involved in liver steatosis is carbohydrate response element binding protein (ChREBP), whose activity is induced by a high carbohydrate diet, insulin[37] and ethanol[38]. It increases the expression of both lipogenic enzymes (such as fatty acid synthase) and glycolytic ones[39]. The effect of HCV on ChREBP is not known, to our knowledge.

(3) Peroxisome proliferator-activated receptor (PPAR)-γ is another master transcription factor involved in fat metabolism. Increased activity of PPAR-γ is associated with an increase in lipid synthesis[40] and is seen in patients with liver steatosis. It upregulates genes involved in lipid synthesis, increasing the activity of mediators such as SREBP-1, fatty acid synthase and acetyl coenzyme a carboxylase, all of them leading to increased hepatocyte lipid content.

Interestingly, PPAR-γ is related to increased expression of genes that regulate the synthesis of adipose differentiation related protein[41], which functions to coat lipid droplets within liver cells[42]. It has been shown that HCV core protein increases the transcriptional activity of PPARgamma, although it exerted no effect on PPARgamma gene expression[43].

Synthesis of triglycerides is a complex process, in which several enzymes participate. During fasting, the increased flux of fatty acids to the liver increases the translocation of lipin-1, a protein with dual activity on fatty acid metabolism[44]. Lipin proteins translocate from the cytosol to the endoplasmic reticulum where they show phosphatidate phosphatase (PAP 1) activity. This enzymatic activity transforms diacylglycerol 3 phosphate into diacylglycerol (DAG), which serves as substrate for triglyceride and phopholipid synthesis. Fatty acids are added to the DAG molecule through the action of acyl coenzyme A:diacylglycerol acyltransferase to form triglycerides[45].

In addition to its PAP 1 activity, lipin also translocates to the nucleus, where it enhances expression of genes involved in fatty acid oxidation[46]. This requires interaction with PPAR-α and PPAR-γ coactivator 1α, forming a physical complex. This leads to decreased intracellular levels of fatty acids which defends the cell from the damaging effect of these molecules[47,48].

Consistent with its effect on free fatty acids, insulin stimulates the activity of lipin-1 by unknown mechanisms, and obesity-related insulin resistance down-regulates lipin gene expression[49]. PAP 1 activity is enhanced in ethanol-induced liver steatosis[50], but lipin deficiency may exacerbate ethanol-associated liver steatosis-perhaps by impairment of fatty acid oxidation[51]. Concordantly, ethanol up-regulates lipin-1 gene expression[52]. Liver lipin is also regulated by SIRT-1[53], a molecule whose activity is inhibited by ethanol. However, to our knowledge, the effect of HCV on lipin proteins has not been analysed.

Inhibition of fatty acid oxidation

Fatty acid oxidation takes place mainly in the mitochondria, although in a small proportion it also includes microsomal ω- and peroxisomal β-oxidation. Improper fatty acid oxidation may also contribute to liver steatosis. As mentioned earlier, AMPK stimulates hepatic fatty acid oxidation and ketogenesis, since it lowers malonyl-CoA liver content, thereby permitting fatty acid transport to the mitochondria, where they suffer oxidation[30]. Ethanol exerts an inhibitory effect on AMPK[54] and HCV also downregulates AMPK[29]. In a study performed on 30 patients infected with HCV it was found that mitochondrial β-oxidation of fatty acids was impaired and that this impairment was related to serum levels of HCV core protein[8]. Therefore, both in alcoholic and non alcoholic fatty liver disease impaired fatty acid oxidation plays an crucial role, without the need of accompanying mechanisms. However, insulin resistance and proinflammatory cytokines also exert major effects

on this mechanism.

Insulin resistance

Normally, insulin activates acetyl CoA-carboxylase, leading to the formation of malonyl-CoA, which inhibits mitochondrial fatty acid oxidation; it also strongly inhibits gluconeogenesis by blocking key enzymes such as phosphoenolpyruvate carboxykinase and glucose 6 phosphatase. Additionally, it inhibits lipolysis and promotes glycogen synthesis and *de novo* fat synthesis using carbohydrates as substrate. Finally, it favours SREBP and ChREBP transcription, as was mentioned above. Therefore, it exerts lipogenic effects on the liver cell[55]. Insulin action takes place after binding to a specific receptor, which, upon activation, leads to the phosphorylation of a series of inactive kinases called insulin responsive substrates (IRS), transforming them into active ones. Some final effects of this complex cascade of kinases include phosphorylation of transcription factors, such as forkhead box protein (FOX)O1 and FOXA2, among others[56]. Phosphorylated FOXO1 is unable to activate transcription of key enzymes involved in gluconeogenesis, such as phosphenolpyruvate carboxy-kinase or glucose 6 phosphatase, and thus, liver production of glucose is blocked[57]. Another transcription factor-FOXA2- is involved in hepatic fatty acid oxidation[58].

In states of insulin resistance, insulin fails to phosphorylate FOXO1 and therefore, it fails to block gluconeogenesis. Therefore, fasting hyperglycaemia is observed despite hyperinsulinism and lipolysis is also activated, leading to an increase in the fatty acid load to the liver. However, the expected decrease in liver triglyceride synthesis is not observed. This is interpreted as a result of the stimulatory effect of insulin on SREBP-1c, favouring triglyceride synthesis. Therefore, insulin resistance is selective[59]: the lack of inhibition of gluconeogenesis leads to hyperglycaemia and in turn hyperglycaemia leads to increased insulin secretion, but SREBP activity is enhanced, leading to increased triglyceride synthesis. Other factors that are mentioned below may possibly aid in explaining this paradox.

In normal conditions, insulin not only has an adipogenic effect on the hepatocyte but it also limits VLDL secretion[60]. This effect is mainly dependent on an insulin-derived increased rate of degradation of apoprotein (apo) B but it is also due to the inhibition of apo B 100 synthesis. This preserves the triglycerides stored in the hepatocytes from utilization in the postprandrial state, so that they do not compete with the exogenous fatty acids. Apo B synthesis is a necessary step for VLDL formation. Newly synthesized apo B translocates into the endoplasmic reticulum and encounters MTP, among other chaperone proteins[61]. Importantly, FOXO1 enhances MTP expression[62]. This may explain why in conditions associated with insulin resistance the postprandrial decrease in VLDL secretion does not take place, and why hypertriglyceridemia constitutes a feature of the metabolic syndrome. As mentioned earlier, HCV is able to modulate MTP activation, directly promoting steatosis[9,63]. A recently described orphan receptor protein (orphan receptor small heterodimer partner) also plays an important role in the development of liver steatosis, although precise mechanisms are still unknown[64]. It possibly represses transcriptional activation of MTP; HCV increases its expression[65].

HCV also directly provokes insulin resistance. In HCV infection, insulin resistance is more closely related to viral load than to obesity, supporting a direct effect of HCV on insulin metabolism[66]. In fact, diabetes is more frequently observed among HCV patients[67]. The mechanisms involved in insulin resistance seem to be genotype-specific. It has been shown that HCV non-structural protein 5A (NS5A) is able to phosphorylate serine residues of IRS-1, thereby interfering with the post receptor downstream cascade of insulin action[68]. In accordance with this fact, treatment of HCV patients with pegylated interferon and ribavirin reduces insulin resistance assessed by homeostasis model for assessment[69]. Moreover, NS5A protein also exerts direct lipogenic effect through activation of LXRs[70].

In addition to the effect of non-structural proteins, it has been recently shown that HCV 1 and 4 core proteins are able to alter the degradation of IRS-1 and IRS-2 in a pathway dependent on suppressor of cytokine signalling 3 (SOCS3), thus also altering insulin signalling[71,72] by stimulating ubiquitination and subsequent degradation of IRS. Moreover, Pazienza *et al*[73], in 2007, showed that core protein of genotype 3a promoted IRS degradation by down-regulation of PPAR γ and up-regulation of SOCS7, whereas the core protein of genotype 1b activated the mammalian target of rapamycin (mTOR). Activation of mTOR leads to insulin resistance[74], but also exerts a direct effect on SREBP-1, leading to increased lipid synthesis. Some authors believe that the main mediator of increased lipogenesis in conditions characterized by insulin resistance is mTOR, acting on SREBP[75].

Fat as an endocrine organ: Cytokines

We have seen that steatosis ultimately depends upon the fatty acids pool, mainly derived from adipose tissue. It is also important to keep in mind that fat is not only a source of free fatty acids, but also a source of pro-inflammatory and anti-inflammatory cytokines which are able to modulate the circulation of free fatty acids from fat tissue to liver and again from liver to peripheral tissues[76]. These cytokines are also involved in some key steps of the progressive liver damage observed in individuals affected by steatohepatitis. To add more complexity to this scenario, recent research has shown that fat tissue is not homogeneous. Trunk fat is associated with increased insulin resistance and vascular risk[77], whereas leg fat exerts opposite effects[78]. These differences probably reflect the secretion of a different cytokine profile. In general, trunk fat has a

"negative" cytokine profile: it secretes less adiponectin, a "protective" cytokine, but more TNF and interleukin (IL)-6 than in the gynoid profile of fat distribution (fat around the hips and legs which is associated with increased production of adiponectin)[79]. Therefore, it is important to analyse the diverse fat compartments when studying the influence of these cytokines on liver steatosis. The cytokine profile associated with hepatitis C-liver steatosis, and the potential role of these cytokines on liver fat deposition is controversial[80-82] as well as their relationships with histological changes in chronic HCV infection.

Although cytokines are definitely involved in the inflammatory process which marks the evolution from steatosis to steatohepatitis, they also play a role in simple steatosis, both by aggravating it directly, or by affecting the metabolic axis which controls fatty acid trafficking. For instance, TNF-α is involved in SREBP activation[24]. On the contrary adiponectin activates fatty acid oxidation[83,84], but decreases the activity of fatty acid synthase and acetylcoenzyme A carboxylase[85]. Moreover, it inhibits liver production of TNF[86]. By upregulation of AMP activated protein kinase activity it also influences other pathways involved in lipid metabolism decreasing SREBP-1 and up-regulating PPAR-α in several tissues[87], an effect which is shared by IL-6[88]. PPAR-α is a transcription factor for several genes involved in the transport, oxidation, and export of free fatty acids[89,90]. It can be viewed as a sensor of intracellular free fatty acids, since it becomes activated by intracellular free fatty acids. PPAR-α deficiency promotes the development of fatty liver, and its activity is altered by classic factors involved in liver steatosis, such as ethanol consumption and HCV infection. Chronic ethanol feeding inhibits PPAR-α function due to the effect of acetaldehyde, which inhibits transcriptional activation of PPAR-α[91]. HCV causes down-regulation of PPAR-α[92], and is able to inhibit its activity by inducing repression of PPAR-α signaling by micro RNA-27b[93].

Leptin, another fat-derived cytokine, may promote fibrogenesis through up-regulation of transforming growth factor-β[94], but it also protects the liver from fat accumulation by lowering the expression of SREBP-1[95]. These nearly opposite effects may explain, perhaps, disparate findings in relation to leptin levels in chronic HCV infection[96]. Increased leptin levels, but also normal[97] or even decreased ones[98] have been reported in chronic HCV infection and leptin may[99] or may not be related to liver steatosis[96,100] in chronic HCV infection.

Increased trunk fat is not the only factor responsible for increased cytokine secretion in HCV infection. Increased reactive oxygen species (ROS)-which also directly impair mitochondrial oxidation of fatty acids[101] activate nuclear factor kappa B (NFκB), a key transcription factor for the expression of cytokines[102] such as TNF-α or IL-6, among others. In addition to the many proinflammatory effects of TNF-α, it also causes insulin resistance and liver steatosis by inhibiting IRS[103]. Excessive ROS production depends on the intracellular effect of HCV. NS3 and 5A are able to activate mitochondrial ROS production by altering calcium trafficking at the endoplasmic reticulum membrane[104]. This altered calcium influx also triggers increased transcription of STAT-3 and NFκB, leading to increased cytokine production which closes a positive feed-back loop. In addition, NS3 and NS 5A are also able to stimulate toll-like receptor-4, in a way similarly to that caused by the lipopolysaccharide in the initial stages of alcoholic hepatitis[105]. Furthermore, LXR, which can be directly activated by HCV, regulates a set of genes that encode proinflammatory mediators[43].

CONCLUSION

Liver steatosis is a very complex process, in which many proteins and enzymes are involved. As shown, viral proteins may affect several of the metabolic pathways leading to simple steatosis, including cytokine activation. Indeed, cytokine production takes place even at early stages, and, among many other questions outlined in this review, it remains to be answered why, despite early cytokine activation, only some patients evolve to steatohepatitis, a key step in the progression of HCV-induced liver damage.

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P- Reviewer: Dehghani SM, Pavlidis C, Snyder N
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Liu SQ

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