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**Lipid dysregulation in hepatitis C virus, and impact of statin therapy upon clinical outcomes**

Simon TG *et al*. Lipid dysregulation in chronic hepatitis C infection

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**Abstract**

The hepatitis C virus (HCV) is one of the most common causes of chronic liver disease and the leading indication for liver transplantation worldwide. Every aspect of the HCV life cycle is closely tied to human lipid metabolism. The virus circulates as a lipid-rich particle, utilizing lipoprotein cell receptors to gain entry into the hepatocyte. It has also been shown to upregulate lipid biosynthesis and impair lipid degradation, resulting in significant intracellular lipid accumulation and circulating hypocholesterolemia. Patients with chronic hepatitis C (CHC) are at increased risk of hepatic steatosis, fibrosis, and cardiovascular disease including accelerated atherosclerosis. HMG CoA Reductase inhibitors, or statins, have been shown to play an important role in the modulation of hepatic steatosis and fibrosis, and recent attention has focused upon their potential therapeutic role in CHC. This article reviews the hepatitis C viral life cycle as it impacts host lipoproteins and lipid metabolism. It then describes the pathogenesis of HCV-related hepatic steatosis, hypocholesterolemia and atherosclerosis, and finally describes the promising anti-viral and anti-fibrotic effects of statins, for the treatment of CHC.

**Key words:** Hepatitis C virus; Lipid profiles; Cholesterol; Statin; Fibrosis; Cirrhosis

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**Core tip:** This article reviews the complex relationship between hepatitis C virus (HCV) infection and human lipid metabolism. It discusses the aspects of the hepatitis C viral life cycle that are entwined with cholesterol homeostasis, as well as the clinical implications of HCV-mediated changes in human lipid profiles. Finally, it describes the current state of knowledge regarding the impact of statin medications on histological, virological and clinical outcomes, among patients with chronic hepatitis C.

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**Introduction**

Hepatitis C virus (HCV) is a single-stranded RNA virus, of the genus *Hepacivirus* and the family *Flaviviridae*. Affecting 2% to 3% of the global population, HCV is one of the most common causes of chronic liver disease and the leading indication for liver transplantation worldwide[[1](#_ENREF_1),[2](#_ENREF_2)]. Estimates suggest that over a period of twenty to thirty years, cirrhosis will develop in 10% to 25% of patients with untreated or relapsed chronic hepatitis C (CHC), and hepatocellular carcinoma (HCC) in 1% to 5%[[2](#_ENREF_2)].

Hepatic steatosis is a common histopathological finding in patients with CHC. Various factors have been independently associated with steatosis, including obesity, diabetes, hyperlipidemia and alcohol consumption[[3](#_ENREF_3)]. It has also been demonstrated that the hepatitis C virus possesses a unique relationship with host lipids and lipoproteins[[4](#_ENREF_4),[5](#_ENREF_5)], and relies heavily on host lipoproteins, lipid droplets, and host co-factors for each step of the viral life cycle including the facilitation of viral replication[[6-8](#_ENREF_6)]. At the same time, HCV causes profound lipid perturbations within the infected host, resulting in hepatic steatosis, circulating hypocholesterolemia and increased atherogenesis[[6](#_ENREF_6),[8-12](#_ENREF_8)].

Statins, which inhibit the rate-limiting enzyme of the mevalonate pathway, HMG CoA Reductase, have been shown to play an important role in the modulation of hepatic steatosis and cholesterol metabolism, and recent attention has focused upon their potential therapeutic role for patients with CHC. This article reviews the molecular pathways of lipid homeostasis and the pathogenesis of hepatic steatosis as they relate to chronic hepatitis C infection, and then describes the potential impact of statin medications upon clinical, viral and histological outcomes.

***HCV viral life cycle and host lipoproteins***

HCV infection begins with attachment of the viral particle to the hepatocyte cell surface, in a process that requires many host proteins that are closely entwined with lipid metabolism[[13-16](#_ENREF_13)]. To enter the cell, HCV must then associate with multiple cell surface receptors, three of which are closely linked to lipoprotein metabolism: the scavenger receptor class B member 1 (SRB1) protein, the Neimann-Pick C1 Like 1 (NPC1L1) receptor, and the low-density lipoprotein receptor (LDLR). The HCV viral life cycle is shown in Figures 1 and 2.

SRB1 is a cell surface transmembrane protein, primarily expressed in the liver and steroidogenic tissues. Although its essential function is cholesteryl ester uptake from HDL, it also serves as a multi-ligand receptor for various lipoproteins, including VLDL, LDL and HDL[[17](#_ENREF_17)]. Oxidized LDL and VLDL have been shown to inhibit HCV cell entry[[18](#_ENREF_18)], while HDL enhances HCV entry in an SRB1-dependent process[[19-21](#_ENREF_19)]. Changes in circulating lipid levels have indeed been shown to impact both viremia and treatment response: increased triglyceride levels have been linked to improved viral clearance[[22](#_ENREF_22)], while elevated LDL and total cholesterol is associated with improved treatment response to interferon-based therapy[[23](#_ENREF_23)].

The NPC1L1 receptor is a cholesterol receptor in the intestines and the liver, essential for dietary cholesterol absorption and biliary cholesterol reabsorption. It is thought to promote HCV cell entry *via* interaction with cholesterol of lipoviral particles and by modulation of cholesterol homeostasis, which in turn alters membrane composition and affects HCV cell entry[[24](#_ENREF_24)]. *In vitro*, inhibition of NPC1L1 blocks initiation of HCV infection, *via* a cholesterol-dependent mechanism occurring before virion-cell membrane fusion[[25](#_ENREF_25)]. A recent *in vivo* mouse model also showed that blockade of NPC1L1 with ezetimibe blocks viral cell entry[[24](#_ENREF_24)].

LDLR is a transmembrane glycoprotein responsible for the uptake of serum lipoproteins[[26](#_ENREF_26)]. Transcription of LDLR is upregulated by the sterol-regulatory element binding proteins (SREBPs)[[26](#_ENREF_26),[27](#_ENREF_27)], and the signaling molecules PCSK9[[28](#_ENREF_28),[29](#_ENREF_29)], and inhibited by the inducible degrader of LDLR (IDOL)[[30](#_ENREF_30),[31](#_ENREF_31)]. It has been shown that accumulation of HCV RNA within hepatocytes correlates with the expression of LDLR, and that antibodies directed against LDLR inhibit the cellular absorption of HCV[[25](#_ENREF_25),[32](#_ENREF_32)]. HCV has also been shown to activate SREBP-mediated PI3-K/AKT and LXR pathways[[10](#_ENREF_10)], resulting in further activation of LDLR, and thus enhancing viral infectivity.

Once inside the cytoplasm, the uncoated viral genome is translated, and the polypeptide is cleaved into 10 viral proteins. The HCV structural proteins (E1, E2 and core) play important roles in viral replication and assembly, while the non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) are essential for the intracellular aspects of the viral life cycle[[33](#_ENREF_33)]. Following translation, the viral genome is transcribed by the proteins NS3 and NS5B[[34](#_ENREF_34)]. HCV core protein accumulates around lipid droplets (LD), which are stores of triaglycerols and cholesterol esters[[35](#_ENREF_35)], and has been shown to inhibit the activity of MTP (microsomal triacylglycerol transfer protein) and the subsequent secretion of very low-density lipoprotein (VLDL)[[36](#_ENREF_36)]. The functions of each viral protein and their interactions with host lipid metabolism are outlined in Table 1.

HCV RNA replication and assembly of the LVP occur at the membranous web (MW), a specialized structure composed of clusters of viral vesicles and lipid droplets (LD)[[37](#_ENREF_37),[38](#_ENREF_38)], on which the LVP and viral proteins converge[[39](#_ENREF_39),[40](#_ENREF_40)]. The enzyme diacylglycerol transferase-1 (DGAT) facilitates the trafficking of core, NS5A and NS4B proteins to the LD[[41](#_ENREF_41),[42](#_ENREF_42)], and results in inhibition of triglyceride lipolysis and lipid droplet turnover, thus increasing the concentration of available intracellular lipids, for the facilitation of further HCV replication[[43](#_ENREF_43)]. To export new HCV virions, the virus co-opts the host VLDL synthesis and secretion pathways. Synthesis of VLDL involves the generation of a VLDL precursor, using the lipid transfer function of the microsomal triglyceride transfer protein (MTP), which lipidates nascent apolipoprotein B100 (apoB100)[[44](#_ENREF_44)]. The VLDL precursor is then targeted to the Golgi apparatus for export. The viral LVP is enriched in ApoE and ApoB, and thus possesses characteristics of a VLDL particle. This enables it to utilize the lipid transfer function of the MTP, and thus co-opt the VLDL secretion pathway and facilitate virion export[[6](#_ENREF_6),[45-48](#_ENREF_45)].

***Lipid changes in chronic hepatitis C infection***

**Circulating hypocholesterolemia:** Circulating lipid levels are altered in patients with HCV, regardless of the duration of infection. In a cohort of patients with acute HCV, early infection was associated with reduction in LDL and total cholesterol levels; following viral eradication through spontaneous clearance or successful anti-HCV treatment, the lipids of those patients returned to pre-infection levels[[49](#_ENREF_49)]. Patients with CHC also have demonstrate reduced levels of circulating LDL, apolipoprotein B100 (apoB) and total cholesterol, compared to healthy controls[[50](#_ENREF_50)]. An inverse relationship has also been described between reduction in apoB levels and HCV viral load, among those with non-genotype 1 infection[[50](#_ENREF_50)]. These perturbations also seem to resolve after successful clearance of CHC[[49](#_ENREF_49)], supporting the hypothesis that HCV has a direct cytopathic effect upon host lipid metabolism.

The presence and degree of hypocholesterolemia carries important prognostic implications for patients with CHC. Elevated LDL and high-density lipoprotein (HDL) levels have been associated with improved rates of sustained virologic response (SVR)[[51](#_ENREF_51),[52](#_ENREF_52)]. This may be related to the dependence of HCV upon LDL cholesterol concentrations and the LDLR for both cellular entry and viral replication.

**Hepatic steatosis:** Hepatic steatosis is frequently observed in the setting of CHC[[53](#_ENREF_53)], and is thought to result from a combination of viral-mediated activation of lipid biosynthesis pathways and reduced lipid export[[54](#_ENREF_54), [55](#_ENREF_55)]. The presence of hepatic steatosis among patients with CHC has been associated with poor treatment response [lower sustained viral response (SVR) rates] and accelerated disease progression to advanced fibrosis and cirrhosis[[56-58](#_ENREF_56)]. Both patient-related factors and viral factors play important roles in the modulation of HCV-related steatosis.

One important viral factor that impacts host lipid metabolism is viral genotype. Genotype 3 CHC is associated with the greatest degree of hepatic steatosis, and the most significant reductions in serum cholesterol levels[[50](#_ENREF_50),[59](#_ENREF_59)]. In the fasting state, patients with genotype 3 demonstrate profoundly elevated cholesterol metabolites[[60](#_ENREF_60)], as well as increased intracellular lipid accumulation[[47](#_ENREF_47),[61](#_ENREF_61),[62](#_ENREF_62)], compared to all other HCV genotypes. In contrast, among patients infected with all other genotypes of CHC, metabolic risk factors, including insulin levels, diabetes and obesity, appear to play a more important role in progressive steatosis[[63](#_ENREF_63),[64](#_ENREF_64)]. This was demonstrated in analyses linking hepatic steatosis to higher levels of circulating viremia, among genotype 3 patients[[65](#_ENREF_65)]; in those cohorts, the eradication of infection resulted in improvement or resolution of steatosis, a finding not seen in other genotypes[[66](#_ENREF_66)].

Patient factors that modulate hepatic steatosis include genetic variations and metabolic dysregulation. Patients with a single nucleotide polymorphism (SNP) in the interleukin 28B (*IL28B*) gene (genotype CC) possess lower serum levels of triglycerides, higher LDL-C levels[[67](#_ENREF_67)], and an overall reduced prevalence of hepatic steatosis[[68](#_ENREF_68)]. The IL-28B CC genotype has also been associated with increased rates of SVR[[69](#_ENREF_69),[70](#_ENREF_70)]. In addition, an independent genome-wide association study also determined that a single genetic variant (I148M) in the human patatin-like phospholipase domain containing 3 (PNPLA3) rs738409 C>G SNP was the strongest genetic determinant of hepatic steatosis[[71](#_ENREF_71)].

In multiple subsequent candidate gene studies, PNPLA3 I148M has been shown to specifically influence hepatitis C-related liver fat accumulation[[72-74](#_ENREF_72)], as well as NASH[[75](#_ENREF_75),[76](#_ENREF_76)], fibrosis progression[[77](#_ENREF_77)] and hepatocellular carcinoma[[78](#_ENREF_78)]. However, unlike IL28B, PNPLA3 has consistently not been shown to influence SVR[[73](#_ENREF_73),[79](#_ENREF_79)]. These findings were recently confirmed in a post-hoc analysis of a large randomized trial of patients with genotype 1 CHC, where PNPLA3 again was associated with progressive steatosis and development of fibrosis, but not with SVR[[73](#_ENREF_73)]. Interestingly, the authors observed that this was modulated by the IL28B polymorphism, suggesting new complexity to the relationship between genotype variations and disease progression[[73](#_ENREF_73)]. Further research will be needed to fully characterize the mechanisms that underpin the associations between these risk alleles and hepatic steatosis.

Additional patient-related determinants of hepatic steatosis in CHC include alcohol use[[74](#_ENREF_74)] and metabolic derangements, particularly insulin resistance, diabetes and the metabolic syndrome[[64](#_ENREF_64)]. The link between hepatitis C and insulin resistance has also been supported in multiple population-based cohort studies, where adults with CHC were three to eleven times more likely to develop type 2 diabetes[[80](#_ENREF_80)], compared to uninfected controls.

**Accelerated atherogenesis:** Hypocholesterolemia and lower rates of systemic hypertension do not seem to protect patients with HCV infection from atherosclerosis. Ishizaka and colleagues first demonstrated a link between HCV and carotid artery plaque formation[[81](#_ENREF_81)], and it has since been demonstrated that HCV seropositivity is an independent risk factor for coronary artery disease (CAD), over and above traditional risk factors including age, smoking status, hypertension, diabetes and hyperlipidemia[[82](#_ENREF_82),[83](#_ENREF_83)]. Although some studies have yielded conflicting results, with some confirming[[84](#_ENREF_84)] and others refuting[[85](#_ENREF_85)] this link, convincing recent data has nevertheless shown excess cardiovascular mortality during the course of chronic HCV infection[[86](#_ENREF_86),[87](#_ENREF_87)]. Indeed, a recent review concluded that HCV infection should be considered a risk factor for the development of atherosclerosis, and argued for more vigilant preventive cardiac screening in this population[[88](#_ENREF_88)].

***potential therapeutic role of statin medications***

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), are among the most commonly prescribed medications worldwide, and have been shown to be safe in chronic liver disease[[89](#_ENREF_89),[90](#_ENREF_90)]. There is mounting evidence that statins exert powerful pleiotropic effects *via* both HMG-CoA dependent and independent pathways, modulating inflammation, angiogensis, apoptosis and cell growth[[89](#_ENREF_89),[91-98](#_ENREF_91)]. Several studies have also shown that statins may inhibit HCV replication, and thus may exert powerful anti-HCV effects as well.

**Effect of statins on viral replication:** Statins appear to block HCV replication by inhibiting *de novo* cholesterol and geranylgeranylated protein synthesis, thus reducing expression of key HCV viral proteins and inhibiting pro-inflammatory signaling pathways[[99](#_ENREF_99),[100](#_ENREF_100)]. In early in vitro studies, cells cultured with lovastatin successfully inhibited HCV RNA replication[[101](#_ENREF_101),[102](#_ENREF_102)]. This was confirmed in a high-throughput screen of small molecule modulators of HCV replication, with the strongest antiviral activity observed in atorvastatin, fluvastatin and simvastatin[[103](#_ENREF_103)]. It is thought that the geranylgeranyl lipid product of the mevalonate pathway is necessary for HCV replication[[7](#_ENREF_7),[104](#_ENREF_104),[105](#_ENREF_105)]. In experiments with lovastatin, the statin-mediated inhibition of HCV replication was overcome by the addition of geranylgeraniol, but not by farnesol or cholesterol[[7](#_ENREF_7),[104](#_ENREF_104)], results which underscored the importance of the mevalonate pathway in HCV replication.

Despite negative results from *in vivo* analyses of statin monotherapy[[106](#_ENREF_106),[107](#_ENREF_107)], a great deal of evidence now suggests a beneficial role of statins upon virologic outcomes in patients treated with pegylated interferon (IFN) and ribavirin[[52](#_ENREF_52),[108](#_ENREF_108),[109](#_ENREF_109)]. In a large retrospective cohort of 8293 veterans undergoing anti-HCV therapy, statin use was an independent predictor of SVR[[108](#_ENREF_108)]. In a subsequent uncontrolled, prospective Japanese pilot study of patients infected with genotype 1b, fluvastatin also was associated with improved SVR[[110](#_ENREF_110)]. Since that time several randomized controlled trials have demonstrated that statins increase SVR rates when combined with peginterferon and ribavirin in genotype 1 infection[[111](#_ENREF_111)]. Despite this compelling evidence, the future importance of statins for the enhancement of SVR is uncertain as we enter the era of second-generation and novel direct acting antiviral (DAA) therapy for CHC, which yields SVR rates of over 90%.

**Anti-fibrotic effects of statins:** It has also been postulated that statins may exert antifibrotic effects, although the data are more limited. Animal models show that statin use blocks the activation of hepatic myofibroblasts, inducing apoptosis and preventing both proliferation of hepatic stellate cells (HSCs) and their production of collagens[[95](#_ENREF_95),[97](#_ENREF_97),[98](#_ENREF_98),[112-114](#_ENREF_112)]. Until recently, reports in humans consisted primarily of retrospective studies of laboratory markers of hepatotoxicity, and were limited by small sample sizes, lack of appropriate controls or histological data from liver biopsy, which remains the gold standard for the assessment of fibrosis[[90](#_ENREF_90),[115](#_ENREF_115),[116](#_ENREF_116)]. However, in a recent post-hoc analysis of a large, prospective human trial of patients with advanced CHC followed with serial liver biopsies, it was demonstrated that statin use was associated with significantly reduced fibrosis scores[[117](#_ENREF_117),[118](#_ENREF_118)].

**HCC:** Mounting evidence also suggests that statins offer chemoprevention against many malignancies, including HCC[[91](#_ENREF_91),[119-123](#_ENREF_119)]. They inhibit cell growth, tumor spread, and appear to exert powerful antiproliferative, antiangiogenic and immunomodulatory effects[[96-98](#_ENREF_96)]. One mechanism is *via* direct interference with lipid rafts, thus inhibiting cell signaling, tumor invasion and angiogenesis[[124](#_ENREF_124),[125](#_ENREF_125)]. *Via* competitive inhibition of HMG-CoA reductase, statins prevent post-translational prenylation of the Ras/Rho superfamily, which are otherwise upregulated in approximately 30% of neoplasms[[96](#_ENREF_96),[120](#_ENREF_120)]. By decreasing expression of MMP-14 and TIMP-2, statins also inhibit the PI3K/PTEN/AKT/mTOR pathway, blocking tumor cell spread[[96-98](#_ENREF_96),[112](#_ENREF_112)].

In a recent population-based cohort of patients infected with HCV, statin users were shown to have a significant reduction in the incidence of HCC[[126](#_ENREF_126)]. The results were statin-specific, and both dose and duration responses were seen, with a hazard ratio of 0.33 for HCC among those taking higher cumulative daily doses. These results are consistent with several other large observational studies[[127](#_ENREF_127),[128](#_ENREF_128)]. Randomized data, however, does not appear to support the relationship between statins and reduced risk of HCC. In a pooled meta-analysis pooling of 7 observational cohorts and 26 randomized controlled trials, the authors found a 37% reduced risk of HCC among statin users in the observational studies (adjusted odds ratio 0.52, 95%CI: 0.42-0.64), but no benefit attributable to statins in the randomized groups[[123](#_ENREF_123)]. Such differences between observational studies and randomized trials may reflect length of follow-up, patient selection, lack of sufficient power to detect a difference, within a selected cohort.

**Statins in the era of DAA therapy:** The role of statins as adjunctive therapy in HCV treatment has so far been limited to the previous standard of care, pegylated interferon and ribavirin. It is unknown what benefit, if any, statins may confer to those patients treated with the new DAA medications. Although statins have been shown to be independent predictors of SVR in both Boceprevir and Telepravir-based trials, with SVR rates > 90% in the majority of treated patients, the additive benefit of statin therapy is less substantial, than that seen with IFN and Ribavirin. Moreover, concerns have been raised about the potential for significant drug interactions between statins and DAAs[[129](#_ENREF_129)]; at this time, simvastatin, lovastatin and atorvastatin are contraindicated for use with telaprevir[[130](#_ENREF_130),[131](#_ENREF_131)], and both simvastatin and lovastatin are contraindicated with boceprevir[[132](#_ENREF_132)]. As noted above, there is likely little additive benefit with statins for SVR, as new DAAs demonstrate SVR rates above 95%, however future studies are needed to fully characterize the role of statins for delaying or preventing fibrosis, cirrhosis or the development of HCC.

**Conclusion**

Every aspect of the HCV life cycle is closely linked to human lipid metabolism. Not only does the virus itself circulate as a lipid-rich particle that mimics VLDL, it also utilizes cell surface receptors essential for lipid metabolism to gain entry into the hepatocyte. Once inside the cell, the virus upregulates intracellular lipid synthesis, impairs lipid degradation, and decreases catabolism and export of lipoproteins. As a result, it causes significant intracellular lipid accumulation as well as a relative circulating hypocholesterolemia. Patients with chronic HCV infection are at increased risk of developing hepatic steatosis, fibrosis, and cardiovascular disease including accelerated atherosclerosis. Statins, which inhibit the rate-limiting enzyme of the mevalonate pathway, HMG CoA Reductase, have been shown to play an important role in the modulation of hepatic steatosis and fibrosis, and it is postulated that they may also possess important anti-proliferative, anti-angiogenic and antioxidant effects, with a potential protective role against the development of HCC. It remains to be seen to what degree statin medications will play a role in adjunctive management of patients with CHC in the era of new DAAs.

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**Table 1 Functions of hepatitis C virus structural and non-structural proteins**

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| --- |
| **Structural proteins** |
| Protein | Function | Association with Lipid Metabolism |
| E1 | Surface envelope protein of LVP | Enriched around lipid droplet |
| E2 | Surface envelope protein of LVP, binds CD81 for viral fusion and cell entry | Interacts with ApoE and SRB1 facilitating lipid transfers around LD  |
| Core | Important for cell surface binding, replication and assembly | Increases expression of SREBP, FASN. Colocalizes with apoB.  |
| **Non-structural proteins** |
| Protein | Function | Association with Lipid Metabolism |
| P7 | Creates transmembrane ion channel in membranous web, (viroporin) | Assists in recruitment of core protein to LD by DGAT1. |
| NS2 | Cysteine protease | Increases expression of FASN, SREBP |
| NS3 | Serine protease, RNA helicase, promotes viral protein processing with NS4A | Unknown |
| NS4A | Protease; cofactor for NS3 | Uknown |
| NS4B | Directs membrane rearrangements for formation of membranous web | Activates fatty acid synthase, associates with DGAT1 and P14KA, facilitating creation of membranous web |
| NS5A | Phosphoprotein, required for replication, forms bridge to assembly | Activates FASN; associates with P14KA, DGAT1 |
| NS5B | RNA-dependent RNA polymerase, for replication of viral genome | Direct interaction with fatty acid synthase gene |

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**Figure 1 hepatitis C virus viral life cycle.** hepatitis C virus (HCV) entry into human hepatocytes is a complex, multi-step process that takes place at the basolateral region of polarized hepatocytes. It begins when the viral particle binds surface glycosaminoglycans (GAGs) and the low-density lipoprotein receptor (LDLR) *via* apolipoprotein E. This is followed by a complex series of interactions mediated by cellular factors including scavenger receptor class B type I (SR-BI), the tetraspanin CD81, claudin-1 (CLDN1), occludin (OCLN), the Niemann-Pick C1-like 1 (NPC1L1) receptor, as well as receptor tyrosine kinases (RTKs) that promote CD81–CLDN1 association and membrane fusion. The HCV particle is then internalized into the hepatocyte by clathrin-mediated endocytosis.



**Figure 2 hepatitis C virus-mediated perturbations in cholesterol metabolism.** Hcv: Hepatitis C virus.