In Vitro Interaction between Hepatitis C Virus (HCV) Envelope Glycoprotein E2 and Serum Lipoproteins (LPs) Results in Enhanced Cellular Binding of Both HCV E2 and LPs

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Hepatitis C virus (HCV) particles in serum associate with lipoproteins (LPs), and the low-density lipoprotein receptor (LDLr) has been implicated in virus attachment and entry into cells. To clarify the basis of interactions between virus and LPS, we determined whether HCV interacts with human LPS via its envelope glycoprotein E2. The binding of serum-derived virus-like particles, HCV E2, and HCV E2–LP complexes to CD81 and LDLr was studied. Incubation of HCV E2 protein with human and bovine LPS (very low density, low density, and high density) enhanced the binding of both HCV E2 and LPS to CD4+ lymphoblastoid (MOLT-4) cells, foreskin fibroblasts, and hepatocytes. The binding of HCV E2 to MOLT-4 cells was not enhanced when it was preincubated with lipid-free apoprotein B, which suggests that E2 interacts with the lipid moiety of human lipoproteins. The LP interaction was specific for HCV E2—incubation of HIV gp120 with LPS did not enhance gp120 binding to MOLT-4 cells. The enhanced HCV E2 binding required expression of both human CD81 and LDLr. These data suggest that HCV E2 associates with LDL and that the resulting complex enhances binding of both ligands to cells, which may contribute to the finding that HCV-infected individuals have significantly lower levels of LDL than control subjects.

Hepatitis C virus (HCV) infection is a common cause of morbidity and mortality worldwide (reviewed in [1]). Approximately 80% of infections persist, and 20% of persistent infections progress to chronic liver disease [2]. Because of the long duration between infection and the development of serious liver damage, it has been predicted that there will be a marked increase in liver disease resulting from HCV over the course of the next 25 years [1]. The mechanism(s) by which HCV attaches to and enters cells is not clear. Recombinant HCV envelope glycoprotein (E2) interacts directly with several cell-surface receptors—including CD81 [3], the scavenger receptor B1 [4], DC-SIGN, and L-SIGN [5, 6]—which has led to speculation that these cell-surface molecules may represent components of an HCV cellular receptor complex [3, 7–10]. HCV E2 has consistently been shown to bind CD81, and the presence of CD81 is required, although not sufficient for infectivity of both HCV-pseudotyped retroviruses (HCVpp) [11–13] and cell-culture infectious HCV (HCVcc) [14–16]. CD81 is a member of the tetraspanin family of cell-surface molecules and is expressed on virtually all nucleated cells [17].

HCV exists in different forms in the circulation of infected individuals, and electron-microscopic studies...
of serum from HCV-infected individuals have demonstrated considerable heterogeneity in particle size, with diameters ranging from 20 to 100 nm [18–20]. This heterogeneity has been explained by the presence of different species of HCV, ranging from nonenveloped and enveloped particles to HCV-associated with serum components such as lipoproteins (LPs) and immunoglobulins [18, 20–25]. Material in serum that contains HCV RNA, presumably virus particles, associates with LPs that sediment in sucrose gradients at the buoyant densities of very low density LPs (VLDLs) and low-density LPs (LDLs), ≤1.06 g/cm³ [7, 21, 23–27]. VLDL is synthesized by the liver and consists of triglycerides, cholesterol, phospholipids, and the apoprotein (apo) B100. The enzymatic digestion of VLDLs in plasma results in intermediate-density LPs (IDLs) and LDLs. The LDL receptor (LDLR) recognizes both apoB100 and apoE and thus binds LDLs, VLDLs, IDLs, and chylomicron remnants [28].

HCV RNA, HCV core protein, and IgG are all found in sucrose-gradient fractions that contain VLDL and LDL particles (densities ≤1.06 g/cm³) [18, 20], and Andre et al. [18] and Petit et al. [20] found that virionlipoparticles have distinctive morphological characteristics when they are examined by electron microscopy. In addition to these low-density HCV particles, particles containing HCV RNA that have densities of 1.11–1.18 and >1.32 g/cm³ have been described [22, 23]. Chimp-panzee infectivity studies have demonstrated that only the very low density HCV particles were infectious, whereas the higher density particles were not [22, 29]. Similarly, the low-density HCV particles in plasma bound to cells, whereas the intermediate-density HCV particles did not [26]. Recombinant HCV virus-like particles (VLPs) expressed by baculoviruses [30, 31], HCVpps [11–13], and HCVccs [14–16] have heterogeneous buoyant densities, and the predominant species of particles are found at densities between 1.11 and 1.18 g/cm³. Nevertheless, HCVpps and HCVccs are infectious in cell-culture systems. The differences between these in vitro HCV particle types and HCV particles found in serum from infected humans are not completely understood. The predominant density of VLPs is similar to the intermediate-density HCV particle type found in plasma from infected humans, and it is possible that these particles may not share critical structural aspects of infectious HCV particles found in serum from HCV-infected individuals.

HCV in plasma coprecipitates with LDLs [24, 25], and Monazahian et al. [7] demonstrated that the expression of recombinant human LDLr in murine cells lacking human CD81 conferred binding of HCV to these cells. Although recombinant HCV E2 specifically binds to CD81 [3, 26], the cell binding of plasma-derived, low-density HCV particles was not inhibited by soluble human CD81, and the extent of virus binding and entry correlated with the expression of LDLr [26]. Plasma-
Figure 2. Hepatitis C virus (HCV) E2 binding to cells. HCV E2 protein mixed with human low-density lipoprotein (LDL) demonstrated enhanced E2 binding to MOLT-4 cells (A, B, and C). Cell-bound E2 was detected by an anti-E2 monoclonal antibody (anti-HCV MAb; A and B) or an anti-E2 polyclonal antibody (anti-HCV PAb; C). Human MAb against HIV gp120 served as the isotype control antibody (IC; A and B). The effect was specific for HCV E2—fluorescently labeled HIV gp120 (gp120*) preincubated with human LDL did not result in enhanced gp120 binding (A). Fluorescent-labeled control protein (Ctrl) provided background fluorescence levels (A). Preincubation of HCV E2 with LDL (E+L) also increased E2 binding to Huh-7 cells (D). When cells were preincubated with anti–LDL receptor (anti-L), a dose-dependent inhibition of E2 binding was observed (D). *P<.05 vs. IC samples; †P<.05 vs. E2 protein without LDL; ‡P<.05 vs. 2.5 μg/mL LDL.

MATERIALS AND METHODS

HCV and mock preparations. Plasma was obtained from patients with HCV-related chronic liver disease or from HCV antibody–negative and HCV RNA–negative control subjects as described elsewhere [36]. Very low density (≤1.07 g/mL) and intermediate-density (1.12–1.18 g/mL) HCV particles were separated by sucrose-gradient centrifugation at 156,000 g for 72 h at 6°C, as described elsewhere [23, 36]. Negative control plasma (mock) samples were prepared in the same manner. The study was approved by the University of Iowa’s institutional review board, and all subjects provided informed consent.

Proteins and antibodies. Purified recombinant HCV envelope glycoprotein E2 (Ala 384–Lys 715) expressed in CHO cells was obtained from Austral Biologicals. HIVgp120–fluorescein isothiocyanate (FITC) was obtained from Bartels. Human and murine soluble CD81 (provided by Dr. Shoshana Levy, Stanford University, Stanford, CA); human LDL and labeled human LDL–BODIPY 488 (Molecular Probes); human VLDL, LDL, and HDL (Biodesign); and bovine LDL (Sigma) were used in these studies. Unless otherwise specified the concentration of E2 was 2.5 μg/mL, and that of LDL, VLDL, and HDL was 20 μg/mL.

Anti–HCV E2 human monoclonal antibody (MAb) 108 and

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Figure 3. Low-density lipoprotein (LDL) binding to MOLT-4 cells. Labeled LDL (LDL*) bound to MOLT-4 cells, and binding increased when LDL* was mixed with hepatitis C virus E2 protein (2.5 μg/mL) before its addition to cells (see Materials and Methods). The concentration of LDL is given in micrograms per milliliter (1, 5, or 10). *P<.01 vs. no LDL* cells; †P<.05 vs. cells incubated with only 1 μg/mL LDL*/well.

human anti–HCV E2 polyclonal antibodies (PAb) were used as described elsewhere [26, 37] for the detection of HCV E2 bound to cells. Anti–HIV gp120 human MAb F105 (NIH AIDS Reagent Repository; provided by Marshall Posner, Harvard Medical School, Boston, MA), goat anti-LDL Pa and normal goat antibody (Sigma), anti–human LDL MAb (clone 4G3), and anti–human LDL receptor (clone C7) were provided by Dr. Jheem Medh (California State University, Long Beach, CA), anti–human CD81 MAb (clone JS64; Research Diagnostics) and nonspecific mouse IgG (Zymed) were used in these studies. Species-specific fluorescent-labeled secondary antibodies were obtained from Molecular Probes. Nonspecific background binding was determined using isotype-control antibodies.

ELISA. Microwell plates were coated with 4G3 anti-LDL MAb (4 μg/mL in 100 mmol/L bicarbonate buffer [pH 9.6]) overnight at room temperature. After washing with Tris-buffered saline (TBS; 150 mmol/L NaCl and 20 mmol/L Tris-HCl [pH 7.5]) and blocking by the addition of 150 μL of Blotto (TBS plus 0.1% Tween 20, 2.5% normal goat serum, and 2.5% nonfat dry milk) for 1 h at room temperature, plates were washed, and E2 protein or E2 protein with LDL in PBS was added. After incubation overnight at room temperature, plates were washed before the addition of anti–HCV E2 MAb 108 (7.5 μg/mL) for 1.5 h. Plates were again washed and incubated with anti–human IgG–alkaline phosphatase conjugate (Promega) in Blotto (at a concentration of 1:5000 for 1 h at room temperature). Wells were washed and incubated with p-nitrophenyl phosphate (1 mg/mL) for 30 min. Absorbance was measured at 405 nm using a multiwell plate reader.

Cell lines. A CD4+ T lymphoblastoid cell line (MOLT-4) and a hepatocyte cell line (Huh7) were obtained from American Type Culture Collection. Human foreskin fibroblasts (FSFs) and LDLr-deficient FSFs (null) were provided by Dr. Jheem Medh [26]. MOLT-4 cells were cultured in RPMI 1640; human fibroblasts and human Huh7 cells were propagated in Dulbecco’s modified Eagle medium (DMEM). Media were supplemented with 10% fetal calf serum (FCS), 100 U/mL penicillin, 100 μg/mL streptomycin sulfate, and 2 mmol/L L-glutamine, unless otherwise specified Mouse 3T3 cells and 3T3 cells expressing human CD81 [38] were cultured in DMEM that contained 10% FCS, 100 U/mL penicillin, 100 μg/mL streptomycin sulfate, 2 mmol/L L-glutamine, and 0.1 mg/mL neomycin.

Binding assay. Recombinant HCV E2 protein or HIV-gp120–FITC, human or bovine LPs, HCV, or mock virus preparations were added to cells for 60 min at 4°C. Cells were washed and incubated with the appropriate ligand-specific antibody for 60 min at 4°C. Antibody binding was detected using goat anti–human IgG–Oregon green (10 μg/mL) for 45 min at 4°C. Cells were washed 2 times, fixed in PBS that contained 4% paraformaldehyde, and analyzed by flow cytometry (FACScan; Becton Dickinson). A total of 10,000 cells was analyzed for each experiment, and all experiments were repeated a minimum of 3 times, with consistent results.

Statistical analysis. All statistical analyses were performed using SigmaStat software (version 2.03S; Jandel Scientific) All sample comparisons used Student’s t test to compare mean fluorescence intensity (MFI).

RESULTS

Low-density fractions (≤1.06 g/cm³) were prepared using plasma from HCV-infected or -uninfected donors and were incubated with MOLT-4 cells at 4°C. Cell-bound virus was detected by flow cytometry using anti–HCV E2 MAbs and PAbs (figs 1A and 1B). The MFI for binding for the HCV-specific antibodies using the mock control preparation was the same
Figure 4. Human CD81 and human low-density lipoprotein receptor (LDLr) expression in hepatitis C virus (HCV) E2 cell binding. A, The amount of human CD81 expression on murine 3T3 and 3T3+CD81 cells. *P < 0.01 vs. isotype control. B, HCV E2 binding onto to cells expressing human CD81 and not enhanced in the presence of LDL. †P < 0.05 for E2 detected on CD81 cells vs. 3T3 cells without CD81. C, HCV E2 protein binding to human foreskin fibroblasts expressing both CD81 and LDLr (white bars) and to fibroblasts expressing only CD81 (LDLr deficient; black bars). LDL enhancement of E2 binding was only observed in cells expressing LDLr; ‡. P < 0.01.

as the MFI when isotype control antibodies were used with either preparation (data not shown). The amount of LDL bound to cells was reproducibly higher in HCV preparations than in HCV-negative controls (P < 0.01) (figure 1C), even though the serum LDL cholesterol levels of individuals who provided samples were similar (104 and 105 g/dL, respectively). To examine the possibility that this observation might be related to interactions between E2 and LDL, an LDL-E2 ELISA was developed using purified HCV E2 and LDL. Wells were coated with a murine anti-LDL MAb, and HCV E2 with or without LDL was added as described in Materials and Methods. Bound HCV E2 was detected using human anti–HCV E2 MAb, and E2 was detected only in the wells in which E2 had been preincubated with LDL (figure 1D). The extent of E2 captured was directly correlated with the LDL concentration used.

Because E2 interactions with human CD81 were shown to vary depending on the context of CD81 presentation [9, 39], we evaluated the influence of LDL on E2 binding to MOLT-4 cells. HCV-E2 was incubated with increasing concentrations of human LDL for 1 h at 4°C before the addition of HCV E2-LP complexes or E2 alone to MOLT-4 and Huh7 cells. After incubation (for 1 h at 4°C), cells were washed, and HCV E2 binding was detected using flow cytometry. HCV-E2 binding to MOLT-4 cells was reproducibly increased when LDL was added to HCV E2 before incubation with cells (figure 2A). The enhanced binding was specific for HCV E2—there was no increased binding of an unrelated viral envelope glycoprotein (HIV gp120) incubated with LDL under identical circumstances (figure 2A). Saturation was observed at LDL concentrations of 5 μg/mL (figure 2B). Increased E2 binding in the presence of
Figure 5. Hepatitis C virus (HCV) E2 cell binding when mixed with apoprotein B100 (AB), very low density, low-density, and high-density human lipoprotein (VLDL, LDL, and HDL, respectively) and with bovine LDL (BLDL). Preincubation of HCV E2 with purified AB (A and B) did not alter the amount of E2 bound to MOLT-4 cells, even though AB binding was observed (A). When E2 was preincubated with human VLDL, LDL, and HDL, E2 binding increased (B). Similarly, HCV E2 binding increased after incubation with (C). *P<.01 vs. E2 without lipoprotein. HCV E2 was detected by anti-HCV monoclonal antibody (MAb). LDL binding was detected by goat anti-LDL serum (anti-LDL) with appropriate isotype control (IC) serum or human MAb (see Materials and Methods).

LDL was seen when either an anti-HCV MAb (figu e 2A and 2B) or an anti-HCV PAb (figu e 2C) was used for the detection method. Thus, the observation does not appear to be related to alterations in antibody affinity. Enhanced E2 binding was also observed when Huh7 cells were used (figu e 2D). To determine whether the enhanced binding was specific for LDL and required LDLr, cells were preincubated with isotype control or anti-LDLr MAb before the addition of E2-LP complexes. A dose-dependent reduction in enhanced E2 binding was observed (figu e 2D).

To ensure that enhanced LDL binding was not due to nonspecific antibody interactions, HCV-E2 and fluorescent-labeled LDL was incubated for 1 h at 4°C and added to MOLT-4 cells for an additional hour. Cells were washed and analyzed for labeled-LDL binding. LDL binding was saturated at concentrations ≥5 μg/mL; however, at LDL concentrations below saturation (1 μg/mL), the addition of HCV E2 resulted in an increase in MFI from 14.6 to 78.8 (figu e 3) (P<.001). Enhanced LDL binding in the presence of HCV-E2 was also detected when E2–unlabeled LDL complexes were detected with a goat anti-LDL PAb; however, when a murine anti-LDL MAb (4G3) was used to detect LDL binding, enhanced LDL binding was not observed (data not shown). This finding is consistent with our previous data showing that the LDL-E2 complex was not detected by the 4G3 MAb in an immunodot assay [26].

The increase in binding of both E2 and LDL to MOLT-4 cells may be due to an association between LDL and HCV E2 that enables the resulting complex to bind to either the LDLr or CD81. To examine this further, mouse 3T3 cells expressing only murine CD81 or cells expressing both murine and human
Figure 6. Effect of medium-associated lipoprotein removal on low-density lipoprotein (LDL) and hepatitis C virus (HCV) E2 binding. MOLT-4 cells were treated with dextran sulfate (or sham treated) before the addition of fluorescent-labeled LDL or control protein (LDL*; A). *Mean fluorescence shown is one-tenth the measured value (actual value, 214 fluorescence units). After the removal of medium-associated lipoproteins with dextran sulfate (Dex), HCV E2 binding was lower (B). E2 binding was restored by incubation of the cells in medium that contained 10% fetal calf serum, as described in Materials and Methods (Rescue). When HCV E2 was preincubated with human LDL, E2 binding was enhanced under all conditions. *P < .01 vs. basal and rescue values; †P < .01 vs. E2 without LDL.

CD81 were studied [38]. 3T3 cells transduced with the CD81 retrovirus vector expressed high levels of human CD81 on the cell surface, whereas the control 3T3 cells did not (fig. 4A). HCV E2 only bound 3T3 cells expressing human CD81 (fig. e 4B); however, preincubation of HCV-E2 with LDLs did not increase the amount of cell-bound HCV E2. Thus, the enhanced E2 binding that occurs after incubation with LDL appears to require the expression of human LDLr. Consistent with this, HCV E2 bound to normal human FSFs and to human fibroblasts that lack human LDLr (fig. e 4C). Only cells expressing LDLr demonstrated an increase in HCV E2 binding when they were preincubated with LDLs. Thus, human CD81 expression was necessary for HCV E2 cell binding, and the increase in E2 binding that occurred after E2 was mixed with LDL required human LDLr and human CD81. We reproducibly observed a reduction in the amount of E2 bound to FSFs that were deficient in LDLr, compared with those with LDLr, even though high levels of CD81 were present in both cell lines (data not shown). This may reflect E2 bound to lipids present in FCS that are adherent to LDLr-positive cells (see below).

To determine whether HCV E2 interacts with the apoprotein or lipid moiety of human LPs, we evaluated apoprotein B (apoB) binding to the human LDLr using a PAb against LDL (fig. e 5A). Preincubation of HCV E2 with apoB did not increase the amount of cell-bound E2, which suggests that the interaction between E2 and LDL does not directly involve the apoprotein component. To determine whether HCV E2 interacts with LPs other than LDL, HCV E2 was preincubated with human VLDL, LDL, and HDL, and bovine LPs (fig. e 5B and 5C). The amount of E2 bound to MOLT-4 cells increased with all human LPs (fig. e 5B) and with bovine LDL (fig. e 5C). The finding that apoB did not interact with E2 and that E2
interacts with multiple classes and species of LPs suggests that HCV E2 interacts with the lipid moiety of the LPs (figure 5) and that bovine FCS-derived LPs binds to human LDLr.

In all published studies of HCV or HCV E2 binding, cells were grown in medium that contained LP-rich FCS. To assess the role that FCS plays in E2 binding, fluorescent-labeled LDL was added to MOLT-4 cells before or after the removal of cell-bound LPs. After dextran sulfate treatment to remove LPs [40], significantly more labeled LDL bound to cells, compared with untreated cells (figure 6A). HCV E2 binding to MOLT-4 cells decreased after dextran sulfate treatment (figure 6B), which suggests that E2 binding involves cell-bound bovine lipids from medium with FCS. When dextran sulfate–treated cells were washed and placed in medium that contained 10% FCS for 30 min at 37°C before the addition of E2, the amount of E2 bound to cells was partially rescued (figure 6B). Furthermore, when E2 and LDL were mixed before the addition to the cells, E2 binding was enhanced independently of the treatment of cells with dextran sulfate.

**DISCUSSION**

HCV in serum is found in association with low-density LPs (VLDL and LDL); however, there are limited data describing direct interactions between HCV or HCV E2-LP complexes with LDLr. Using coimmunoprecipitation methods, Monazahian et al. [33] demonstrated interactions between recombinant HCV envelope proteins E1 and E2 and human, but not bovine, LDLs and HDLs. We speculate that the differences in E2 antigen, antibodies, and methods used to detect interactions all may contribute to why we found an interaction between E2 and bovine lipids and Monazahian et al. did not. Lambot et al. [34] also demonstrated an interaction between recombinant HCV E1 and E2 proteins and liposomes, which confirms the interaction of HCV envelope glycoproteins with lipids. We found that more LDLs from HCV-infected individuals bound to cells than LDLs from HCV-negative individuals with the same serum concentration of LDLs (figure 1). Consequently, we investigated interactions between HCV E2 protein (aa 384–715) and LPs and assessed the cell binding of E2, LP, and E2-LP complexes.

We confirmed that HCV E2 protein interacted with LDL, VLDL, and HDL [33], and we assessed these complexes in cell-binding and ELISA studies. Both E2 and LDL binding increased when they were mixed together before their addition to lymphotrophic (MOLT-4), hepatic (Huh-7), and FSF cell lines. Human CD81 expression was necessary for E2 binding even in the presence of lipids—HCV E2 did not bind murine 3T3 cells unless human CD81 was expressed on the cell surface (figure 4). However, the expression of human LDLr was necessary for enhanced E2-LP binding, given that murine cells expressing human CD81 and murine LDLr and human cells lacking LDLr did not demonstrate enhanced E2 binding when E2 was complexed with LDLs (figure 4). The findings that bovine LPs bound to human LDLr, interacted with HCV E2, and influence HCV E2 binding to cells (figure 6) complicates the interpretation of HCV E2 or HCV binding assays, because HCV E2 binding was decreased when cells were treated with dextran sulfate for the removal of lipids. Figure 7 illustrates a model that could explain these findings. Both CD81 and LDLr are expressed on most human cells; thus, neither explains the hepatotropism of HCV.
However, the liver is the main site of VLDL synthesis (>95%) and uptake (>40%) [28]. The hypothesis that the assembly of infectious HCV particles is linked to VLDL synthesis would potentially explain the hepatotropicity of HCV. It is also likely that unidentifiable hepatocyte-specific factor(s) are required for HCV entry [11–16].

The interaction between HCV E2 and LDL did not appear to be based on protein–protein interactions, because E2 binding was not increased after incubation with apoB (fig e 5A). The fact that preincubation of E2 with all forms of the human LPs (VLDL, LDL, and HDL) and with bovine LDL resulted in increased E2 binding to MOLT-4 cells further suggests that E2 interacts with the lipid moiety of LPs (fig e 5B). ApoB100 is present in VLDL and LDL, whereas apoE is present in VLDL and HDL. Both apoB and apoE are ligands of human LDLr, perhaps explaining the increased binding of E2 after incubation with HDL. Alternatively, HDL has been shown to facilitate HCVpp binding to cells by virtue of interactions with the scavenger receptor class B type 1 [41].

The specific infectivity of HCV particles associated with VLDL and LDL is much higher than that of the more dense HCV particle types [27, 42], and HCV particles with buoyant densities of 1.11–1.18 g/cm³ did not bind to cells in vitro [26, 32]. The more dense HCV particles have been suggested to be virus-IgG complexes [22]; however, their presence in patients with a gammaglobulinemia indicates that HCV-IgG complexes do not completely account for these particles [23, 43]. Alternative explanations for the composition of these more dense particles include nucleocapsids and non–lipid-associated enveloped particles [22]. Because HCV E2 interacts with HDLs (fig e 5) [33], the more dense particles may represent HCV-HDL complexes, given that the density of HDL is 1.11–1.17 g/cm³ [28]. The predominant particle species in recombinant HCV VLPs, HCVpp, and HCVcc have buoyant densities in this range [11–16, 30, 31].

HCV appears to have complex interactions with serum components. In addition to interactions with LPs, HCV has been shown to interact with immunoglobulins [44], and an Fc binding domain has been demonstrated on the virus core protein [45]. Up to 80% of individuals with chronic HCV infection have detectable rheumatoid factor in their serum [46], which is far greater than levels seen in individuals with other chronic viral infections, such as HIV or GB virus C. Although the interaction between HCV E2 and human LPs further supports that LDLr plays a role in HCV cell attachment and entry, our results are consistent with those of studies showing that CD81 is required for E2 binding to the cell surface, and our data illustrate that this is true in the presence of LPs. The finding that HCV and HCV E2 enhanced the binding of LDLs to cells may explain the epidemiological observation demonstrating that individuals with chronic HCV infection have lower serum levels of cholesterol and LDL [47–49]. The levels of lower cholesterol found in HCV-infected individuals appear to be specific—individuals with chronic hepatitis B infection did not have significantly lower lipid values than HCV-infected individuals [48]. Furthermore, there was no correlation found between the extent of liver fibrosis in liver biopsy samples and levels of serum cholesterol in HCV-positive individuals [50], which suggests that the low levels of cholesterol and LDL observed in these individuals were not related to decreased VLDL synthesis caused by underlying liver disease.

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References


