MiniReview

Hepatitis C virus core protein: intriguing properties and functional relevance

Ratna B. Ray a,b, Ranjit Ray a,c, *

a Department of Internal Medicine, Saint Louis University, St. Louis, MO 63110, USA
b Department of Pathology, Saint Louis University, St. Louis, MO 63110, USA
c Molecular Microbiology and Immunology, Saint Louis University, St. Louis, MO 63110, USA

Received in revised form 6 June 2001; accepted 6 June 2001
First published online 28 June 2001

Abstract

Hepatitis C virus (HCV) often causes a prolonged and persistent infection, and an association between hepatocellular carcinoma (HCC) and HCV infection has been noted. The pathogenesis of liver damage is at least in part related to virus-mediated factors. Understanding the molecular basis of pathogenesis is a major challenge in gaining insight into HCV-associated disease progression. Recent experimental evidence using HCV cloned genomic regions suggests that the core protein has numerous functional activities. These include its likely role in encapsidation of viral RNA, a regulatory effect on cellular and unrelated viral promoters, interactions with a number of cellular proteins, an modulatory role in programmed cell death or apoptosis under certain conditions, involvement in cell growth promotion and immortalization, induction of HCC in transgenic mice, and a possible immunoregulatory role. These intriguing properties suggest that the core protein, in concert with cellular factors, may contribute to pathogenesis during persistent HCV infection. © 2001 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

Keywords: Hepatitis C virus; Core protein; Gene regulation; Apoptosis; Cell growth regulation; Immune response

1. Introduction

Hepatitis C virus (HCV) causes a spectrum of liver diseases ranging from an asymptomatic carrier state to end-stage disease. The majority of individuals infected by HCV fail to resolve their infection and suffer from chronic hepatitis. Infection with HCV has now been identified as a leading cause of hepatocellular carcinoma (HCC) in many countries around the world. Evidence of an important role for HCV infection includes high seroprevalence of anti-HCV among patients with HCC and documented progression from chronic hepatitis to cirrhosis to HCC. Most of these patients have HCV RNA present in serum as well as in liver tissue and, in many cases, within the tumor itself.

Chronic HCV infection is also associated with autoimmune syndromes, immune complex disorders, and mixed cryoglobulinemia [1]. Unfortunately, a number of important issues related to HCV-mediated disease progression are unknown at this time. The chimpanzee is the only available animal model to study HCV infection; and has been used for characterizing the virus, analyzing the infectivity of clinical samples, and studying clinical and immunological aspects of viral infection. However, spontaneous virus clearance occurs in some chimpanzees following inoculation of HCV [2]. This mimics natural infection in humans, and the virus clearance may be related to host genetic make-up. Analysis of the biological properties related to HCV has proven to be difficult as the virus displays only limited replication in vitro in some cells, including primary human hepatocytes. Despite these obstacles, research over the past decade has revealed significant information on this important viral pathogen, and a number of reviews have eloquently covered diverse aspects of HCV [3–5]. This discussion will focus upon some of the intriguing functional traits of HCV core protein, which are probably not shared by analogous protein of other important human viruses.
2. HCV genome and core protein expression

Sequence divergence of cloned HCV genome from patients indicates several genotypes and a series of subtypes for this virus. An HCV genotypes 1a and 1b are predominant in patients with chronic hepatitis C. The virus genome contains a linear, positive-strand RNA molecule of ~9500 nucleotides, which encodes a single polyprotein precursor of ~3000 amino acid residues [6].

This polyprotein is cleaved by both host and viral proteases to generate at least 10 individual proteins (Fig. 1): Core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B. The structural proteins (Core, E1, E2/p7) are located in the amino-terminal one-fourth of the polyprotein. The genomic region encoding the core protein encompasses amino acids 1–191. Physical association of the core protein with E1 and E2 glycoproteins, most likely taking place in the ER membrane, may have a role in virus morphogenesis. In vitro translation assay from cloned genomic region in the presence or absence of microsomal membrane facilitated the initial characterization of core polypeptides [7,8]. In the absence of microsomal membrane, a polypeptide of ~22 kDa is the primary translated product. Additional polypeptides of higher molecular mass also appear, probably representing complex oligomeric aggregates of core protein. However, in the presence of microsomal membrane, a change in the polypeptide profile of the in vitro translated product is observed. This change is likely derived from a post-translational proteolytic cleavage of the signal peptide located at the carboxy-terminal of the unprocessed core protein. Multimerization of core protein occurs when expressed as recombinant protein. Three different core protein products of ~21, 19 and 16 kDa are generated from HCV genotype 1a [9,10]. The ~16-kDa core protein exists as co-amino-terminal sequence of the ~21-kDa protein, but lacks the carboxy-terminal sequence of ~21-kDa protein. The expression of core protein as a ~16-kDa species is associated with a Lys-9 codon substitution in HCV genotype 1a; however the mechanism for generation of this protein product remains to be understood. On the other hand, a single polypeptide of ~21 kDa or two forms of the core protein, ~21 kDa and 19 kDa, are generated from HCV genotype 1b. Missense mutations at codons 9–11 can occur during chronic HCV infection resulting in expression of an ~16-kDa core protein [11], and an analysis of 10 cases of individuals with HCV-related HCC revealed that three patients have these codon mutations in the core gene. Higher sequence variations within the core are apparent in tumor as compared to non-tumor tissues [12], and the appearance of in-frame stop codons, and deletions leading to frameshifts occur in HCV-associated HCC patients. The secondary or tertiary structure of HCV core protein might be important for specific interaction with viral genomic RNA [13], although the precise length of the core protein species for its likely role in encapsidation of viral RNA is yet to be determined. The core protein of HCV genotype 1a primarily localizes in the cytoplasm [9,10]. However, nuclear localization of the core protein has also been shown in gene-transfected mammalian cells [14] and in the hepatocytes of HCV-infected patients [15]. The carboxy-terminal truncated core protein has been implicated for nuclear localization in some studies. The core protein from HCV genotype 1b accumulates in the nuclei and mitochondria of transgenic mice [16].

Thus, it is not clear at present whether nuclear localization of core protein occurs as a result of frameshift (Jing-Hsiung Ou, personal communication) or truncation of the carboxy-terminus.

3. Cellular gene modulation

The presence of a putative DNA-binding motif, nuclear localization signals, phosphorylation sites, and the nucleocytoplasmic localization of the core protein suggest its possible function as a gene regulatory protein. In vitro studies indicate a role for HCV core protein in the transcriptional regulation of cellular and unrelated viral promoters [8,17,18]. The core protein has been shown to transactivate the human c-myc promoter, IL-2 promoter, Rous sarcoma virus LTR, simian virus 40 early promoter, and suppress the c-fos and human immunodeficiency virus type 1 LTR promoter activities. Interestingly, the core protein either activates or represses promoters depending upon the promoter architecture. Core protein does not appear to bind directly with DNA and may modulate gene expression by interacting with host proteins. Since core protein promotes cell growth regulation (as discussed later), it was of general interest to understand whether this viral protein regulates the activity of the tumor suppressor gene, p53. In vitro studies suggested that HCV core protein transcriptionally downregulates p53 promoter activity [17]. Core protein also represses p21/waf1 promoter activity in vitro. Using mutational analysis, the HCV core protein responsive element in the p21 promoter is mapped downstream of the p53-binding site, suggesting an independent effect of the core protein on p53 and p21. Other
recent reports suggest that core protein physically associates with p53 in vitro and enhances p21/waf1 expression [19,20]. In addition, p53-deficient Hep 3B cells cotransfected with p53 and HCV core gene suppress cell growth [19]. However, HepG2 cells, expressing endogenous p53, when transfected with HCV core gene did not suppress cell growth. Furthermore, in vivo complex formation between p53 and the core protein or colocalization of the core protein with endogenous p53 was not observed [19,20]. Therefore, the biological significance of the association between core protein and p53, and the activation of p21 remains to be understood. Interestingly, results from a clinical study reveals p21/waf1 protein expression is reduced or absent in HCV-related HCC [21]. The reason for the difference of these observations is not clear at present and needs further investigation to understand the precise relationship between core, p21 and p53 proteins in hepatocyte growth regulation.

Nuclear factor \( \kappa \)B (NF-\( \kappa \)B), a transcription factor, binds to the sequence of numerous promoters and enhancers of cellular and viral origin for activation of transcription. NF-\( \kappa \)B responds to inflammatory signals, activates the expression of inflammatory mediators, and displays a role in apoptosis and proliferation. MCF7 cell transfectants expressing the HCV core protein suppress TNF-induced NF-\( \kappa \)B activation [22]. HCV core decreases TNF-induced IxBo degradation which may account for inhibition of NF-\( \kappa \)B activation. Suppression of NF-\( \kappa \)B in HCV core-expressing cells was also observed following treatment with PMA, OA, and \( \mathrm{H}_2\mathrm{O}_2 \). These agents activate NF-\( \kappa \)B through different pathways which are not completely overlapping, and the exact mechanism required to activate NF-\( \kappa \)B is not fully understood. Thus, it appears that the HCV core acts at a step common to all of these inducers of NF-\( \kappa \)B. In fact, the ability of core protein to downregulate NF-\( \kappa \)B expression in the absence of TNF is also evident from an in vitro reporter assay (Ray, R.B., unpublished observation). In contrast, activation of NF-\( \kappa \)B by core protein in the presence of TNF in HepG2 and MCF7 cells have been reported [23]. On the other hand, NF-\( \kappa \)B activation was found to be blocked in core protein expressing murine BC10ME cell line, but not in core-expressing HeLa or HepG2 cells [24]. This difference in observation of NF-\( \kappa \)B modulation may arise from use of stable and transient expression systems and/or the genotype of the virus. The HCV core protein constitutively activates AP-1, which correlates with the activation of JNK and MAPKK [22]. In the presence of a mitogenic signal, HCV core protein enhances Elk1 activation through the downstream region of MEK in the pathway without affecting Elk1 phosphorylation [25]. MAPK pathways play a key role in cell growth regulation and promote transformation. Together, these observations suggest a cell growth-promoting function of HCV core protein.

4. Interaction with cellular proteins

Several groups of investigators have identified cellular proteins associating with HCV core using the yeast two-hybrid interacting cloning system. HCV core protein (Taiwan strain, genotype 1b) associates with the cytoplasmic domain of LT\( \beta \)R and TNFR1 [26]. Lymphotoxin \( \beta \) receptor is a member of the tumor necrosis factor receptor (TNFR) family and is involved in the regulation of lymph node development and possibly other additional immune functions. On the other hand, TNF binds with TNFR1 and may induce the apoptotic signaling pathway. Therefore, the binding of core protein with the TNF family members may have immunomodulatory functions. Recently, Hahn et al. [27] reported that the core protein from HCV genotype 1a (Hutchinson strain) physically binds to Fas in vitro, but not with the cytoplasmic tail of TNFR1. Although, the core protein is well conserved among different HCV genotypes, there are six amino acid differences between the Taiwan and Hutchinson strains, which may contribute to the differences of the above observations [24,27]. HCV core protein binds to heterogeneous nuclear ribonucleoprotein K (hnRNP K), a transcription factor that modulates cell growth regulatory genes, and this association may disrupt hnRNP K-mediated function. HCV core protein also interacts with a putative RNA helicase which belongs to DEAD box family of protein (DDX3, DBX, CAP-R1) [5]. However, the functional significance of the association between core protein and the putative RNA helicase remains to be elucidated. HCV core protein physically associates with the 14-3-3 protein which is an adapter molecule of Ras/Raf/MAP kinase signaling pathway [28]. Introduction of core protein into HepG2 cells increases Raf-1 kinase activity, and may contribute to hepatocyte growth regulation. HCV core protein interacts with the complement p33\( \mathrm{gC}1\qR \) [29]. Since \( \mathrm{gC}1\q \) is displayed on PBMCs, including CD4\( ^{+} \) and CD8\( ^{+} \) T lymphocytes, they are the likely targets of core protein through a direct suppressive effect on T-lymphocyte activation/proliferation. Although the interaction between core and host protein suggests a potential mechanism to alter normal cellular functions, their biological significance in HCV infection is not clear at this time. In most of the yeast two-hybrid screening, a carboxy-terminally truncated core protein has been used as a bait and the interacting proteins bind to the amino-terminal half of the core protein. Recently, the binding of carboxy-terminal half of the core protein with LZZIP, a human bZIP transcription factor, has been observed by screening a human liver cDNA library with the full length core protein (1–191 amino acids) generated from HCV genotype II/1b strain [30]. HCV core protein inhibits LZZIP dependent transcription by sequestering LZZIP in the cytoplasm, and loss of LZZIP function correlates with cellular transformation. Taken together, these observations suggest that core pro-
tein in association with cellular factors may play a role in virus-mediated pathogenesis.

5. Role in apoptotic cell death

Apoptosis is a key element in a host organism’s defense against viral infections, inhibiting viral spread and persistence. To circumvent host defense, viruses have evolved mechanisms which antagonize host death signals so that virus propagation can continue unabated in infected cells. A block of apoptosis could also be critical in the establishment of lifelong persistence in its human host. The mechanism by which HCV maintains viral persistence and promotes HCC is not understood. Since HCV core protein exhibits a gene regulatory role, its potential to modulate the onset of apoptotic cell death has been investigated. Cisplatin, an anticancer agent, induces an apoptotic response and facilitates the study of this phenomenon. In our initial investigation [31], we observed that core protein inhibits cisplatin-mediated apoptosis of human cervical carcinoma (HeLa) cells. Expression of core protein also inhibited cell death attributable to c-myc-mediated apoptosis in Chinese hamster ovarian (CHO) cells [31]. A different study suggested that the core protein induces apoptosis and impairs cell-cycle regulation by activating c-myc expression in CHO-K1 cells [32]. TNF appears to induce multiple antiviral mechanisms, and to synergize with IFN-γ in promoting antiviral activities. Interestingly, HCV core protein suppresses TNF-α-mediated apoptosis in human breast carcinoma (MCF7) and human hepatoblastoma (HepG2) cells [33]. On the other hand, sensitization of TNF-α-mediated apoptosis by core protein in a mouse fibrosarcoma (BC10ME), HepG2 and HeLa cells was observed by Zhu et al. [24]. However, a transgenic mouse line expressing the core protein suggests a reduced sensitivity to TNF [34]. The differences of the results from cell culture studies are presently unclear, and the nature of the experiments, cell types and HCV strains used in these studies may attribute to distinct observations.

The Fas–FasL system has a pathological role in humans, and is involved not only in CTL-mediated cytotoxicity but also in the downregulation of immune responses. Fas is a type I membrane protein of the TNF receptor family, and is ubiquitously expressed in various cells, and potently induces apoptosis by binding with a Fas agonistic antibody or physiological FasL. The FasL predominantly works as a cytotoxic effector molecule of CTLs and NK cells. FasL is cleaved into a soluble form by metalloprotease, and human soluble FasL efficiently induces apoptosis in some Fas-expressing cells. Some patients carrying high levels of soluble FasL in their serum show both hepatitis and neutropenia. A HepG2 cell line constitutively expressing HCV core protein has been shown to sensitize apoptotic cell death upon stimulation with anti-Fas antibody [35]. However, expression of the Fas receptor was not upregulated on the surface of these cells. Core protein may promote Fas-mediated apoptosis of a human T cell line [27]. PBMCs of patients with chronic HCV express a large amount of Fas on the cell surface and these cells become susceptible to stimulation against Fas [36]. The serum levels of soluble Fas ligand (sFasL) are significantly higher in hepatitis C patients and that sFasL level indicates a negative correlation with PBMC numbers. However, a different study [23] suggests that transient expression of the core protein alone or when expressed together with other HCV proteins inhibits Fas-mediated apoptosis in HepG2 and MCF7 cells. These differences may be attributed to transient versus stable expression, and as well as the cell types used in different experiments. Recently, a conditional expression system was developed for the generation of transgenic mice and used to study the Fas signaling effect. Transgenic mice expressing core, E1, E2 and NS2 were resistant to Fas antibody stimulated death with the survival rate correlated with the HCV protein expression levels [37]. Apoptotic cell death in the liver of transgenic mice was significantly reduced compared to control mice. The activation of effector caspase 9 and 3/7 was inhibited in the Fas-mediated apoptotic signaling pathway. Release of cytochrome c from mitochondria was inhibited in HCV protein expressing transgenic mice. However, the contribution of the individual viral proteins to the inhibition of Fas-mediated apoptosis in the transgenic mouse model was not investigated. Thus, different investigators have reported diverse effects of the core protein in cytokine-mediated apoptosis, this requires further in depth analysis.

6. Cell growth regulation

Viral proteins often influence cellular genes, which in turn may be involved in the regulation of oncogenes or tumor suppressor genes. Inactivation of cellular genes is a mechanism for the disruption of normal cell growth. The mechanism by which HCV infection results in HCC is not known. Functional involvement of HCV core protein in cell growth regulation was indicated by the transformation of primary rat embryo fibroblasts (REF) and continuous rodent cells. Although, core protein inhibits p53 promoter activity in vitro, p53 expression appeared to be similar when mRNA from core- and H-ras-transfected REF are compared [17]. Although, this observation is inconsistent with the in vitro studies, it is possible that HCV core protein-mediated repression of p53 may be an early event that precedes cellular transformation. Therefore, p53 expression is no longer relevant in the transformed REF cells. Introduction of core gene into primary human hepatocytes immortalizes cells and display morphology altered to one resembling low-differentiated epithelial cells [38]. Those cells retain an immortalized phenotype and exhibit continuous growth after several passages. Immobilized he-
patocytes exhibited albumin secretion and the presence of HCV core protein. Telomerase expression is reactivated early after senescence and anchorage independent growth is observed in later passages. Thus, HCV core protein appears to be promoting primary human hepatocytes to an immortalized phenotype, which may predispose cells over an extended period of time to undergo a transforming event.

Transgenic animal models have contributed pivotal information on hepatitis virus-mediated pathogenesis. Several transgenic mouse lines expressing HCV structural proteins have been generated. Transgenic C57BL/6xSJL mice generated using a core genomic region from genotype 1a under the control of liver-specific mouse major urinary protein promoter did not exhibit significant liver injury [39]. Western blot analysis of nuclear and cytoplasmic extracts prepared from these transgenic mouse livers indicated that HCV core protein localizes to the cytoplasm in vivo in the mouse hepatocyte and not in the nucleus. Despite the high level of expression detected in Western blot analysis, no immunohistochemical evidence for the presence of HCV core protein could be detected in the liver tissue sections. In vitro studies suggested that core protein binds to lipid droplets containing apolipoprotein A2 in the cells. Analysis of the triglyceride populations within the cells indicates that core protein expression stimulates a change in cellular metabolism of triglycerides. Transgenic C57BL/6 mice were also generated using core gene from genotype 1b under the control of a transcriptional regulatory region from hepatitis B virus. The presence of HCV core protein leads to the development of hepatic steatosis (fatty change) in transgenic mice. After the age of 16 months, transgenic mice developed hepatic tumors that first appeared as adenomas, presenting in a ‘nodule-in-nodule’ manner without cytoplasmic fat droplets [16]. These pathological changes in transgenic mice closely resemble the histopathological characteristics of the early stage of HCC in patients with chronic hepatitis C [40]. A similar level of core protein expression in transgenic mouse livers, and in liver samples from chronic hepatitis C patients has also been observed. However, transgenic mice carrying the envelope genes under the same transcriptional control region did not develop neoplastic lesions in the liver. The mouse strains and the virus genotypes used for generation of transgenic animals by two different groups of investigators [16,39] may contribute to the differences in results. A separate study also suggested that transgenic C57BL/6 mice generated by introduction of the C, E1 and E2 from HCV genotype 1b under the control of H2-K gene promoter developed liver lesions, hepatic necrosis, and altered foci with mitotic hepatocytes around the hepatic central veins, after 10 months of age. However, the transgenic mice generated by introduction of HCV E1 and E2 regions did not reveal pathological changes in liver up to 16 months of age. These data are consistent with and support the hypothesis that the core protein may participate in the pathogenesis of HCV associated diseases. A different study by Kawamura et al. [41] did not suggest pathological changes in the liver within 6 weeks to 6 months of age in FVB transgenic mice expressing core, E1 and E2 proteins of genotype 1b under the control of mouse major urinary protein promoter or albumin promoter. Immunohistochemical analysis revealed a predominantly cytoplasmic presence of core protein with occasional nuclear staining in the transgenic livers. The difference in observation of these studies could be due to the time difference in follow-up of the transgenic mice or the mouse strains used in generation of transgenic animals.

7. Immunological role

Immunity induced by HCV infection appears to be insufficient for protection against reinfection, but the reasons for this are not clear. IgG1 restriction, low titer, and the delayed appearance of an antibody response are observed during HCV infection in patients. Immune evasion and a quasispecies nature are prominent features of HCV [42]. Although, a high rate of genetic variability may facilitate viral escape and persistence in the face of antigen-specific immune responses, HCV protein(s) may also modulate host immunological responses. The cell tropism of HCV has been studied in an attempt to understand the pathogenic events associated with viral infection. HCV replication in both PBMC and bone marrow cells has been documented [43]. A growing body of evidence suggests replication of certain genotypes of HCV, particularly genotype 1, in class II-expressing cells (PBMC subsets). Injection of PBMCs isolated from HCV carriers into SCID mice suggests replication of HCV, which are detected over time in the PBMC of grafted mice [44]. Natural immune responses, both cellular and humoral, are not capable of terminating HCV infection in most humans. Peripheral blood leucocytes may play a role in viral persistence and in antiviral immune responses. HCV core-specific PBMC responses detected in patients with chronic HCV exhibit a decreased type 1 cytokine profile as compared with PBMC from aviremic HCV-infected individuals. Patients with persistent viremia and chronic liver disease have less PBMC showing type 1 cytokine (IL-2, IFN-γ) responses to HCV core protein than patients with self-limited HCV infection [45]. These observations suggest that HCV chronic infection may at least in part be a result of an inability to mount type 1 immune responses. Certain MHC class II alleles are associated with the clearance of circulating HCV [46]. Low IL-12 and low IFN-γ milieu with dendritic cells from HCV-infected individuals suggest that HCV infection may impede the development of CD4+ T cell responses [47]. Significant populations of virus-specific CD8+ lymphocytes are detected at the peak of acute hepatic illness (maximally 3.5% of CD8+ lymphocytes) in...
nine of the patients examined, six of whom failed to clear the virus [48]. Early HCV-specific CD8+ lymphocytes exhibit an activated phenotype in all patients, but this activation is short-lived.

Because core protein is the most conserved HCV structural protein, we evaluated its immunogenic potential as a plasmid DNA in BALB/c mice [49]. A similar experimental approach was undertaken by two other laboratories around the same time [50,51]. Immunization of experimental animals with core plasmid DNA failed to induce a strong CTL activity. These studies have shown < 30% target specific lysis following in vitro stimulation of mouse spleenocytes from hyperimmunized animals. CTL response can be enhanced following DNA immunization along with cytokine-expressing plasmids [51]. Recently, a study using BALB/c mice suggests that immunization with recombinant vaccinia virus expressing HCV core protein suppresses host immune responses, in particular the generation of virus-specific CTLs [52]. These results implied that expression of core protein during HCV infection could account for the low frequency of a CTL precursor observed in chronically infected patients and that the core may play a critical role in the establishment and maintenance of a persistent HCV infection. Suppression of IL-12 and NO in core-expressing macrophages and dendritic cells have also been observed from in vitro studies [53]. The core-expressing cells inhibit proliferation of T cells and IFN-gamma production in mixed lymphocyte reactions. Considering the safety issues involved with the overall properties of the core protein, novel approaches for induction of cellular immune responses, especially CTL generation, are currently under investigation in a number of laboratories. A recent study suggests that core protein adsorbed onto ISCOM (∼1 µM in diameter) primes core-specific CD4+ and CD8+ T cell-mediated immune responses in one of the three immunized rhesus macaques, presumably as a consequence of MHC class I haplotype [54]. Interestingly, the immunized animals had detectable core-specific CTLs in their periphery for more than a year, although the mechanisms involved in the maintenance of memory CTLs are unclear at this time.

8. Conclusion

Knowledge on the function of several HCV proteins, even in the absence of a suitable cell culture system or convenient animal model, has significantly advanced our understanding on the possible HCV-mediated biological effect in an infected host. HCV causes silent disease and the available information on the core protein suggests that its continued presence in persistently infected cells would likely be detrimental for host cells. In fact, the presence of core protein has been detected in chronically infected HCV patients. Whether the observed effects of core protein from ex vivo studies are similar when expressed along with other HCV proteins from a full length cDNA clone remains to be seen. However, ectopic expression of the HCV proteins in the absence of virus morphogenesis may not necessarily mimic the situation exhibited in natural infection. The time span between the observed effects associated with core protein seen in live cells with that of disease progression in a persistently infected host can not be compared. Development of pathological consequences in a host vary depending upon the nature of disease, infecting virus, and the incubation time. Multiple genetic factors, including host innate and acquired immune responses exert distinct characteristics imposed upon the invading organism. Even manipulation of disease in an experimental rodent model takes a longer period for manifestation of disease pathology. Multiple effects of the HCV core protein are summarized in Fig. 2, which may have significant implications for viral persistence and cell growth regulation. However, a more complete understanding of the underlying mechanisms associated with the observed core protein-mediated functions must be addressed. Unraveling the fine-tuned interplay between HCV core and the cellular network leading to the relative functional features associated with HCV infection will likely help to predict the outcome of an infection and in designing appropriate intervention strategies. Finally, HCV exists as a quasispecies, and interpretation of the functional properties of viral proteins with respect to a genotype or subtype merits further consideration. These issues and more will need to be addressed in a field of HCV that continues to evolve.

Acknowledgements

References could not be more extensive cited due to editorial limitations and we apologize to all the researchers.
in this field left unreferenced. We thank SuzAnn Price for preparation of this manuscript. Our research was supported by Grants AI45144, DK5614301, DK58023, and AI45250 from the National Institutes of Health.

References


