Available online at www.elixirpublishers.com (Elixir International Journal)

Virus Research

Elixir Virus Res. 37C (2011) 3864-3871

ISSN: 2229-712X

Hepatic cell injury during HCV infection: a review on the role of various host factors

M. Irshad, Shiwani Singh, M.A.Ansari and Prashant Nag

Clinical Biochemistry Division, Department of Laboratory Medicine, A.I.I.M.S. New Delhi-110029, India.

ARTICLE INFO

Article history:

Received: 14 June 2011;

Received in revised form:

19 July 2011;

Accepted: 29 July 2011;

Keywords

HCV,

Steatosis,

IR,

ROS,

Immunity.

ABSTRACT

The present review deals with the interaction of hepatitis C virus (HCV) with various host factors and the underlying mechanisms involved in liver pathology during HCV infection. The persistence of virus after HCV infection causing chronic hepatitis in high majority of patients was explained in terms of host immune response varying with mutating nature of HCV virus. High scale variability in HCV genome arising of frequent mutation favours HCV to escape immune mediated eradication and to persist in host causing continued liver cell injury. HCV shows pathogenic effect via its role in several metabolic changes and inducing reactive phenomenon including hepatic steatosis, oxidative stress and insulin resistance in HCV infected patients. The structural and non-structural components of HCV virus, particularly, HCV-core, NS3 and NS5A proteins were involved in causing all these reactive state. Moreover, HCV-genotypes showed their varying effect on overall HCV pathogenesis. The HCV core protein from HCV-genotype-3 had close association with causing hepatic steatosis, increasing oxidative stress and inducing insulin resistance in HCV infected patients. All these reactions, ie. hepatic steaotis, oxidative stress and insulin resistance play important role in progression / regression of disease. However, many more studies are still needed to understand it in full measure for developing an effective anti-viral or anti-infection therapy.

Introduction

HCV was first characterized by Choo et al in 1989.[1] It was soon identified as the main causative agent of the previously called post transfusion non-A, non-B hepatitis. HCV is an enveloped RNA virus and belongs to the genus Hepacivirus of the family Flaviviridae. HCV infection is a major cause of chronic liver diseases with about 170 million people infected worldover.[2-4] HCV, a RNA virus has a high degree of heterogeneity[5] that varies 30-35% among different genotypes. Till date six major genotypes and more than 120 subtypes have been characterized[6]. These HCV genotypes have distinct geographic distribution with genotype 1 and 2 frequently occurring worldwide.[7] Genotype 3 is the most prevalent, followed by genotype 1 in India.[8,9] Different genotypes of HCV have important epidemiological implications. In India, approximately 15 million people are HCV seropositive with reported prevalence of HCV in 15% to 20% chronic liver disease (CLD) patients.[10,11]

HCV genome consists of 9.6-kb single-strand RNA of positive polarity and a single open reading frame of 9033 - 9099 nucleotides flanked by a highly conserved 5` and 3` noncoding region (NCR). Its genome codes for a long polyprotein of approximately 3000 amino acids[12] which is processed co-translationally and post-translationally to yield three structural proteins (core, envelope E1, E2 and p7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B).[13] The envelope proteins (E1 and E2) are the outer surface proteins of the virus and have important role in virus entry inside the host cell. NS5B is one of the highly variable regions of HCV genome and codes for a RNA dependant RNA polymerase (RdRp) which lacks proof reading activity. This may alter the detection, sensitivity to anti-viral activity of interferon and pathogenicity of virus.[14]

HCV infection is a major public health problem of the world. It infects approximately 3% world population.[15] HCV infection presents both as asymptomatic as well as symptomatic infection. A high proportion of patients[16] infected with HCV infection develop chronic liver diseases which result in liver cirrhosis and hepatocellular carcinoma (HCC) in later stage.[17] HCV infection is a major indication for liver transplant all over the world.[17] HCV patients show a poor response to antiviral therapy. Moreover, there is a high relapse rate of HCV infection after discontinuation of therapy. Therefore, every effort is being made to understand the pathogenesis of HCV infection so as to create a therapeutic model for an effective treatment against HCV. Present review gives highlights about few host factors (immune etc.) involved and the mechanisms of liver injury caused by HCV infection and its pathogenesis. This includes the role of host immunity, oxidative stress, insulin resistance and steatosis associated with HCV infection. It is believed that an understanding of these phenomenons may help in future plan to resolve the problem of HCV infection.

Role of host immunity vs. HCV

HCV, a blood transmitted virus, reaches liver and infects it for disease causation and viral multiplication. During its course of transmission and final entry to liver cells, host poses several challenges to both its entry in the cell and *in situ* viral proliferation. Host immunity plays very important role in eradication or survival of virus and deciding the course of disease with its acute or chronic manifestation. Whereas some

Tele:

E-mail addresses: drirshad54@yahoo.com

patients develop an acute HCV infection with resolution of disease in a shorter time period, majority of HCV infected patients run a chronic course with persistence of virus for decades and finally development of end stage liver diseases including cirrhosis and hepatocellular carcinoma (HCC). This may be better explained by a sequence of reactions involving onset of HCV and response of host immune system to counter the onset.

Innate Immunity

Innate immunity appears essential and first line defense for control of HCV infections like for several other viral infections. During HCV infection, cells produce Type 1 interferon (IFN) as a result of innate immune signaling events. The secreted IFN induce the cells to resist infection, check viral replication, promote adaptive immunity and activation of Natural Killer (NK) cells, Dendritic Cells (DC) and Kupffer cells etc. Intracellular innate immunity is triggered through host recognition of viral macromolecular motifs, known as pathogen-associated molecular patterns (PAMPs) as non-self by cellular pathogen recognition receptors (PRRs) including Toll-like receptors (TLRs) and Retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs).[18] In hepatocytes RIG-I binds PAMP on HCV-RNA and activates interferon regulatory factor-3 (IRF-3) for expression of IFN-α/β and anti-viral/ interferons stimulated genes (ISGs) that control viral infection. IFN remain major part of innate immunity and are regularly produced in response to viral infection[19] both within infected cells and bystander cells. PAMP-RIG-1 interaction is most upstream to intracellular immunity to produce ISGs and IFN. The secreted IFN and cytokines are responsible for activation of NK, DC and Kupffer cell etc. These cells plays significant role in mounting T/B cell based immunity also.[20] PAMP region lies on 3` UTR of HCV and induces RIG-1 signaling.[21] RIG-1 signaling results in RIG-1 interaction with IFN-beta promoter stimulator (IPS-1) which drives activation of IRF-3 and nuclear factor κB (NFκB).

In majority of HCV infected patients (70-80%), HCV can effectively evade innate immunity resulting in persistent viral infection. This is so because HCV has evolved to counteract the RIG-1 pathway[22] and thus evade the immune challenge. For this, the non-structural proteins of HCV i.e. NS3 and NS4A form a complex which activates NS protease domain to target cleavage of IPS-1. After cleavage, IPS-1 can no longer signal downstream to activate IRF-3 and NFκB and the infected cells no longer produce IFN-β or express ISGs. Thus HCV virions defend them from RIG-1 mediated pathway.[23]

Natural killer (NK) cells, another way of innate immune response, usually becomes activated in an early phase of a HCV infection. Liver is particularly enriched in NK cells. Type-I IFNs activate NK cells. The activated NK cells play an essential role in recruiting virus-specific T cells and inducing antiviral immunity in liver. They also eliminate virus-infected hepatocytes directly by cytolytic mechanisms and indirectly by secreting cytokines including interferon-γ (IFN-γ) and Tumor Necrosis Factor-α (TNF-α), which induce an antiviral state in host cells. Therefore, optimally activated NK cells are important in limiting viral replication in this organ. This notion is supported by the observations that interferon treatment is effective in HCV-infected persons in whom it increases NK cell activity. Surprisingly, HCV has evolved multiple strategies to counter host's NK cell response. Compromised NK cell functions have been reported in chronic HCV-infected individuals. It is interesting to mention that activated NK cells may also contribute toward liver injury.[24]

Cytotoxic T Lymphocytes

During viral infection, T cells recognize viral peptides presented by Major Histocompatibility Complex (MHC) molecules on infected cells. Cellular and viral molecules partly degraded by proteosomes are transported to the endoplasmic reticulum and get associated with MHC molecules which are finally transported to cell surface. These are reviewed by T cells for recognition and their action. Most cytotoxic T lymphocytes (CTL) are $CD8^+$ and recognize antigen presented on MHC class I molecules. However, about 10% of MHC-restricted CTL are $CD4^+$ which recognizes antigen presented on class II molecules. The major role of CTL is the elimination of cells infected with virus. Several viruses have evolved mechanisms to avoid recognition by CTL. They either reduce the expression of MHC molecules or prevent the viral peptide from presentation at the cell surface. CTL plays a part in viral eradication.[25] These cells have been also implicated in the immunopathogenesis of viral infection.[26]

The destruction of HCV-infected hepatocytes releases HCV fragments; these fragments are taken up by myeloid DCs, consequently activating the DCs. These DCs migrate to the draining lymph nodes and express HCV antigens on human leukocyte antigen (HLA) class II molecules. Then, they enhance expression of costimulatory molecules (CD80, CD86) that interact with and activate antigen-specific helper T (Th) cells.[27] In turn, the activated Th cells promote the maturation of DCs by the expression of CD40 ligand and TNF-α.

Dendritic cells induce T-cell activation upon maturation by up-regulation of the expression of their surface molecules, with enhanced antigen presentation capacity and through the increased production of cytokines that stimulate T-cell activation. IL-12 has been shown to play an important role in stimulating IFN-γ production from activated T cells,[28-29] and thus, induces the development of type 1 (Th1) immune response characteristic of CTL activation.

Mature DCs stimulate specific CTLs by antigen presentation on HLA class I molecule and enhance the expression of costimulatory molecules.[27] Cytokines such as IL-2 and IL-12 produced by Th1 cells and DCs further promote CTL activation. These CTLs infiltrate the liver and recognize HCV antigens presented on the surface of HCV-infected hepatocytes together with HLA class I molecules. Then, the effector CTLs release perforin, granzyme, and TNF-α, or express Fas ligand, and initiate a direct attack on HCV-infected hepatocytes.[30-31] Type I IFNs produced by HCV-infected hepatocytes and plasmacytoid DCs (PDC) suppress viral replication by inducing enzymes such as 2′–5′ oligoadenylate synthetase (OAS) and RNA-dependent protein kinase (PKR) in hepatocytes.[32] The plasmacytoid DC recognizes HCV infection through toll-like receptor (TLR)-7, which interacts with single-stranded RNA.[33] The TLR-signaling upregulates PDC-Triggering Receptor Expressed on Myeloid Cells (PDC-TREM) molecules on the cell surface, and PDC-TREM-dependent signal induces further production of IFN-α.[34] Activated OAS destroys viral RNAs, whereas PKR inhibits forming polysome of viral mRNA.[32]

When appropriate CTL responses are induced in hosts, HCV eradication is achieved. However, HCV-specific CTL responses are usually not strong enough to eradicate the virus, hence contributing to persistent infection.

It has become increasingly clear that successful clearance of HCV virus during the acute HCV infection depends on the generation of a vigorous and sustained Th1 type immune response.[35-36] Patients who can mount strong Th1 response showed efficient viral clearance and a self-limited course of disease. In contrast, those who showed defect in IL-12 and IFN-γ production invariably led to viral persistence and chronic hepatitis. Maturation of DC with E2 protein strongly induces IL-12 production from these cells.[27] It is important that an overwhelming majority of the infected persons fail to control the infection and develop a chronic infection with a variable degree of hepatitis and viremia.[2,37] Experimental studies have demonstrated that HCV preferentially induces the expression of antigen processing and IFN-stimulated genes in the infected livers.[38-40]

Impaired function of DCs, which play the crucial role of antigen-presenting cells in inducing immunity, may be responsible for the impaired immune responses. It has been reported that the HCV core, E1, and NS3 proteins inhibit DC maturation.[41,42] HCV is thought to infect DCs through the binding of HCV E2 protein and thereby suppress DC function.[43,44]

The virus-specific CTL kill not only virus-infected cells but also contribute to virus control by noncytolytic mechanisms by secreting cytokines, e.g., IFN-γ, IFN-α/β, and tumor necrosis factor α (TNF-α), which induce an antiviral state in host cells. This makes uninfected cells resistant to infection and frees them from virus by stopping viral replication. The progression of the majority of the infected persons to chronic infection suggests the inability of the antiviral immunity to contain this infection. There may be several reasons for this failure, including emergence of escape variants as a result of a high rate of virus mutations, a decreased production of antiviral cytokines or "stunning" of HCV-specific CTL, a compromised cytolytic potential of the CTL, and antagonistic peptides.[45]

The HCV genome in single host is a dynamic population of different but closely related genomes, designated quasispecies. Hyper variable region-1 (HVR-1) is one of the main contributors to these genetically related variants.[46] In acute resolving hepatitis, HVR-1 shows very little variation in genetic variants, as compared to that in chronic hepatitis.[47] HVR-1 induces anti-HCV neutralizing antibodies[48-49] and HVR-1 specific CD4+ and CD8+ T cells.[50-51] Using the responding host cellular immune response differentially, HVR-1 favours viral escape.[52,53] HVR-1 variations result from the action of a continuous immune-driven positive selection,[54,55] probably controlled by humoral immune responses. Thus, HVR-1 complexity could represent a virus adaptive strategy to escape the continuous selective process mediated by anti-HVR1 antibodies. HCV clearance is associated with a vigorous HCV specific CD4+ and CD8+ T cell response in the acute phase of infection. In contrast, viral persistence is associated with a weak and dysfunctional virus specific T cell response.[52-56] Several possible mechanisms of T cell failure and HCV immune evasion have been proposed and include T cell dysfunction and the emergence of viral escape mutations.[57-58]

Recently, the possible role of different regulatory T cell populations in HCV persistence has also been suggested. There are reports showing higher frequency of CD4+CD25+ regulatory T cells in the blood and CD4+FoxP3+ T cells in the liver of chronically HCV infected patients.[59-61] CD4+CD25+ regulatory T cells suppress HCV specific CD8+ T cell and CD4+ T cell proliferation as well as CD8+ T cell IFN-γ secretion in a dose-dependent and unspecific manner.[59,62-64] Treg cells secrete IL-10 and Transforming Growth Factor- β (TGF-β) after HCV antigen stimulation to show Treg cell mediated suppression of virus specific T cell responses.[63-65] CD4+CD25+ Treg cells obtained from chronically HCV infected patients demonstrated more suppressive activity against HCV specific CD8+ T cells compared to Treg cells isolated from acute HCV infected patients. However the suppressive effect observed in patients who successfully cleared the virus was still significant.[62] Furthermore, another study showed that the frequency of CD4+CD25+FoxP3+ Treg cells and their suppressive capacity against virus specific T cell responses were as high in HCV recovered chimpanzees as in persistently HCV infected chimpanzees.[66] Induction of Treg cells by HCV antigens was demonstrated first time by a response of CD4+ T cell to HCV core protein. HCV specific IL-10 secreting T cells were detected in the blood of chronic HCV infected persons.[67] These regulatory TR1 cells recognized the same epitopes on the core protein as IFN-γ producing TH1 cells. The regulatory CD8+ T cells may play an important role in chronic HCV infection. It is supported by the observation that HCV specific CD8+CD25+FoxP3+ T cells from blood of chronically infected patients suppress HCV specific T cell responses *via* transforming growth factor- β (TGF-β) secretion. The blockade of TGF-β markedly enhanced the HCV specific IFN-γ secretion by CD4+ and CD8+ T cells.[68] The presence of Treg cells, especially in the liver, may also protect the host from tissue damage.

Another important impact of chronic HCV infection on adaptive T cell response is the exhaustion or impairment of HCV-specific CD8+ T cells antiviral function. During chronic HCV infection, CD8+ T cells show their failure to proliferate or secrete antiviral cytokines including interferon-γ (IFN-γ). This phenomenon is promoted by lack of CD4+ T cells and expression of immunomodulatory cytokines like IL-10.[69] The major cause of HCV specific CD8+ T cells impairment is ascribed to expression of inhibitory receptor like Programmed Death-1 (PD-1), Lymphocyte-Activation Gene-3 (LAG-3, a protein related to CD4), CTLA-4 (a member of CD28 receptor family), T-cell immunoglobulin mucin-3 (TIM-3) and 2B4 etc. on HCV-specific CD8+ T cells in blood and liver.[70] Expression of these inhibitory receptors is associated with low levels of CD127 expression and impaired proliferation and differentiation of T cells. Thus, different mechanism contribute to the dysfunction of HCV-specific CD8+ T cells in chronic HCV infection.

HCV Associated Oxidative Stress

Oxidative stress is supposed to be an important part of HCV-induced liver pathogenesis. In studies conducted to explore the role of different molecular components of HCV structure in modulating oxidative stress, it was noticed that HCV-core protein present within the outer membrane of mitochondria induce oxidation of glutathione and promotes Ca^{2+} uptake into mitochondria. Clement et al[68] explained the molecular mechanism by a schematic diagram and demonstrated that following glutathione oxidation, there is increased reactive oxygen species (ROS) production by mitochondrial electron transport complex I and III. The HCV non-structural protein NS5A promotes ROS production in the membrane of endoplasmic reticulum (ER) by activating the release of Ca^{2+} from ER, thereby inducing oxidative stress.[68] NS3 protein induces ROS production by activation of NADPH oxidase.[68]

That HCV infection causes increased ROS production and consequent oxidative stress is evident by presence of markers of increased oxidative stress in the blood. Levels of 8-hydroxy deoxyguanosine and 4-Hydroxy-2-nonenol are increased in HCV infection.[71,72] Similarly, few studies have shown reduced levels of glutathione, possibly used up by antioxidant enzyme glutathione peroxidase, during HCV infection. In yet another study, the serum level of thioredoxin, marker of oxidative stress, was significantly reduced in HCV infection.[73-75]

Although, presence of oxidative stress has been noted in other hepatitis like hepatitis B also, however, there is a remarkable increase in Oxidative Stress (OS) in HCV infection.[71] Several studies conducted at molecular level have shown that structural components of HCV induces an effective OS.[71] HCV-core and non-structural components NS3 and NS5A proteins directly induce OS.[76-79] Core protein is involved in OS generation via oxidation of mitochondria GSH and uptake of Ca^{2+} into mitochondria[79-80] thus, changing the permeability of its membrane.[81] As a result, electron transport complex I increases production of ROS and redistributes cytochrome from mitochondria to cytosolic fraction.[64] NS5A is associated with membrane of ER[82] as mentioned above. NS5A, simultaneously activates even signal transducers transcription and nuclear factor κB (NFκB)[83]All these activations lead to inflammation, immune response and apoptosis.[83,84] Similarly, NS3 triggers ROS by activating NADPH oxidase 2 in mononuclear and polymorphonuclear phagocytes[85] that increase role of apoptosis of hepatocytes.[85] Thus, it is concluded that during HCV infection, the structural and non-structural components of HCV induce significant increase in OS that help in liver damage by following several mechanisms.

HCV Induced Steatosis

Steatosis, a condition with extra fat deposit in liver, is a state leading to liver injury. There are several factors responsible for causing steatosis, including alcohol consumption, obesity, diabetes, etc.[86-88] Studies on steatosis in relation to hepatotropic viruses demonstrated that HCV infection directly causes steatosis in some patients. When these patients are treated with antivirals, steatosis usually disappears. Not only this, there are reports indicating reappearance of steatosis with relapse of infection after end of therapy.[89] Studies in experimental animals have shown that HCV-core protein promotes steatosis in liver.[90-91] Furthermore, when steatosis was studied in relation to HCV-genotypes, it was noticed that although steatosis is induced by all HCV-genotypes, it appears more prominent and frequent with HCV-genotype 3 infection.[92-95] Genotype-3 shows direct involvement in accumulation of triglyceride in hepatocyte. In those patients carrying genotype-3 infection, there is a good correlation between level of steatosis and HCV replication[94,96] and presence of HCV-core in liver.[97] Also steatosis disappears in patient with genotype-3 when treated successfully by anti-viral therapy as compared to those with non-genotype-3 who remain steatotic.[98-99] Steatosis reappears with relapse of infection,[89] clearly supports that HCV-genotypes particular have more steatogenic potential. Subsequent studies[100] indicated that genotype-3 interferes with VLDL secretion. Core protein, which promotes lipid accumulation in hepatocytes,[90,91,101,102] proves more efficient from genotype-3 as compared core from genotype-1. Core protein inhibits microsomal triglyceride transfer protein (MTP) activity, a key protein involved in VLDL assembly, thus leading to steatosis.

Based on various reports, it was concluded that HCV causes steatosis in three different ways : (i) Impaired secretion of lipids from hepatocyte, (ii) Increased de novo synthesis of Free Fatty Acid (FFA) and (iii) Impaired FA degradation. The first aspect of HCV-induced steatosis was proposed as due to the impaired secretion of VLDL. To substantiate it, reports from different studies demonstrated decreased level of Apolipoprotein B (Apo B) and cholesterol in chronic HCV infected patients.[100-103] Their low levels pointed towards HCV disturbing the assembly and secretion of VLDL from the liver. It was further supported by same experimental studies in transgenic mice expressing HCV core protein. These mice had impaired VLDL and Apo-B secretion[104] as compared to non-transgenic mice. Another important aspect in this relation was the evidence of increased de novo synthesis of FFA under the effect of HCV infection. In this context, it is suggested that HCV upregulated the Sterol Regulatory Element Binding Protein-1c (SREBP-1c) signaling pathway[101] with NS2 and NS4B proteins inducing SREBP at transcriptional level.[105-106] It was also induced by expression of HCV core protein.[35] Similarly, investigations on sub-cellular localization of HCV proteins in cells transacted with JFH1 RNA[85] demonstrated core localized to lipid droplets (LDs). Core enhances LDs formation. These studies conducted on JFH1 also indicate genotype-2 to show its involvement in LDs formation and disturbing lipid metabolism. Few studies in chimpanzees infected with HCV also demonstrated that HCV increase activity of lipogenic enzymes like ATP citrate lyase.[107] HCV-core, in particular, activates and helps in cellular lipid synthesis,[107] possibly via its binding with retinoid receptor. However, there is possibility that other viral protein also help in hepatic steatosis via neolipogenesis.

The third important aspect of HCV-induced steatosis is an impaired Fatty Acid (FA) degradation by HCV. Expression of HCV-core protein is reported to reduce the expression of peroxisome proliferation activated receptor-α (PPARα), a nuclear receptor involved in FA degradation and down regulation of mitochondria β-oxidation.[108] Genotype-3 shows significant down-regulation of PPARα as compared to genotype-1.[109-110] It is again HCV-core protein that down regulates PPARα and so, is more effective when from genotype-3 as compared to genotype-1. Core protein from genotype-3 also down-regulated the PPARγ and upregulated suppressor of cytokine signaling-7 (SOCS-7) in Human Hepatoma cells (Huh-7).[111] All these data clearly support that HCV-core protein may modulate the expression of various genes responsible for FA degradation via down regulation of PPARs.

HCV Induced Insulin Resistance (Ir)

HCV is reported to influence several metabolic pathways to increase steatosis, fibrosis, inflammation, apoptosis and insulin resistance[112-114] during disease course. Insulin resistance plays an important role in liver pathogenesis by HCV infection. It has been observed that IR increases the de novo lipogenesis i.e. FA synthesis via over expression and maturation of SREBP-1c, which in turn increases the activities of lipogenic enzymes including Acetyl CoA carboxylase and FA synthase. At the same time, intermediates of triglyceride biosynthesis also activate inhibitors of insulin signaling. For example, activation of protein kinase C (PKC)-E by phosphorylating insulin receptor substrate (IRS-1) and thus inhibiting phosphatidyl inositol 3,4,5 triphosphate (PIP3),[115] inhibiting Akt translocation by ceramides etc.[116] HCV-core protein, either by its direct interaction with insulin signaling pathway or via an increased secretion of TNF-

α is considered to be causing IR.[117-118] The HCV core can activate inhibitors of insulin signaling including mammalian target of rapamycin (mTOR)[111] and SOCS-3 and C-Jun Nterminal kinase (JNK).[119-120] The activation of JNK by HCV core may follow a direct or indirect proinflammatory cytokine mediated mechanism. In conclusion, HCV infection leads to IR in infected patients. IR can lead to steatosis and vice-a-versa and in either case, liver pathology is increased.

Impact

The overall impact of host factors including immune response, oxidative stress, steatosis and IR caused or promoted by HCV infection leads to cause liver damage in different proportion depending on their collective effect. IR promotes steatosis and reduces the response to treatment than steatosis.[121] Though, it is not yet clear, it is assessed that it may be possibly due to deregulation of SOCS-3.[122] Most studies support the theory that IR is an important factor to be considered in HCV infection, both for liver fibrosis and anti-viral treatment. And so, correction of IR appears to be more promising. Another important aspect coming out of all studies till date is the differential inducement of all these causative factors by different HCV-genotypes. At present, there is only preliminary information available regarding the outcome of all these conditions in relation to HCV-genotypes. Once the real impact of each disease causing condition with HCV-genotypes and its isotypes is well established, the preliminary screening for HCV-genotypes may help a lot in predicting the progression of disease and response to treatment, particularly with viewing the impact of above factors.

Conclusion

All above studies finally conclude that it is not any single cause of liver pathogenesis during HCV infection. In fact, host immune response to HCV related peptides and interruptions in the pathways of normal cellular metabolism by all these viral components have a collective role against virus and infected cells. Whereas host immunity is noted to be very crucial and deciding for the acute / chronic course of disease, an inducement of oxidative stress, hepatic steatosis and insulin resistance by HCV protein become the major underlying contributing factors for cellular damage. With an established fact that HCV-genotypes respond differently to anti-viral treatment, their variable role in pathogenic changes becomes an important tool for future research to design therapeutic strategies according to their pathogenic potentials. Though, these studies address some aspects of HCV pathogenesis, however, there is still a lot to unravel the total mystery for an effective anti-HCV therapeutic measure based on well defined pathogenic changes during HCV infection.

Acknowledgement

The authors thank and appreciate the financial aid provided by Indian Council of Medical Research (ICMR), New Delhi, India to conduct this study. Authors are also thankful to Mrs. Suman Rawat for preparing this manuscript.

References

1. Choo QL, Kuo G, Weiner AJ et al. Isolation of a cDNA derived from a blood-borne non-A, non-B hepatitis genome. Science, 1989 ; 244 : 359–362.
2. Lauer GM, Walker BD Hepatitis C virus infection. N. Engl. J. Med., 2001; 345 : 41–52.
3. Hepatitis C: an epidemic for everyone. Available at: www.epidemic.org.
4. World Health Organization Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevalence Board, Antwerp, Belgium. J. Viral Hepatol., 1999 ; 6 : 35–47.
5. Okamoto H, Kural K, Okada S et al. Full length sequence of a hepatitis C virus genome having poor homology to reported isolates: comparative study of four distinct genotypes. Virol., 1992 ; 188 : 331–341.
6. Khaja MN, Munpally SK, Hussain MM et al.. Hepatitis C virus: the Indian scenario. Curr. Sci., 2002 ; 83 : 219–224.
7. Irshad M, Ansari MA, Singh A, Nag P, L Raghavendra, Singh Shiwani, S Sukhbir. HCV-genotypes : A review on their origin, global status, assay system, pathogenecity and response to treatment. Hepatogastroenterol. 2010 ; 57 : 1529 - 1538.
8. Das BR, Kundu B, Khandapkar R et al.. Geographic distribution of hepatitis C virus genotypes in India. Indian J. Pathol. Microbiol., 2002 ; 45 : 323–328.
9. Hissar SS, Goyal A, Kumar M et al. Hepatitis C virus genotype 3 predominates in North and Central India and is associated with significant histopathologic liver disease. J. Med. Virol., 2006 ; 78 : 452–458.
10. Irshad M, Acharya SK, Joshi YK. Prevalence of hepatitis C virus antibodies in the general population and in selected groups of patients in Delhi. Indian J. Med. Res., 1995 ; 102 : 162–164.
11. Chakravarti A, Verma V, Jain M et al. Characteristic of dual infection of hepatitis B and C viruses among patients with chronic liver disease: a study from tertiary care hospital. Trop. Gastroenterol., 2005 ; 26 : 183–187.
12. Bartenschlager R, Lohman V. Replication of hepatitis C virus. J. Gen. Virol., 2000 ; 81 : 1631–1648.
13. Lindenbach BD, Rice CM, eds. Flaviviridae : The viruses and their replication. Philadelphia, PA : Lippincott Williams & Wikins, 2001 ; 991 – 1041.
14. Simmonds P. Variability of hepatitis C virus. Hepatol., 1995 ; 21 : 570–583.
15. Alter MJ. Epidemiology of hepatitis C in the West. Semin. Liver Dis., 1995 ; 15 : 5-14.
16. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J. Viral Hepat., 2006 ; 13 : 34-41.
17. Levrero M. Viral hepatitis and liver cancer: the case of hepatitis C. Oncogene, 2006 ; 25 : 3834-3847.
18. Saito T, Owen DM, Jiang F, et al. Innate immunity induced by composition-dependent RIG-I recognition of hepatitis C virus RNA. Nature. 2008 ; 454(7203) : 523-7.
19. Liu HM, Gale M. Hepatitis C Virus Evasion from RIG-I-Dependent Hepatic Innate Immunity. Gastroenterol Res Pract. 2010 : 548390.
20. Saito T, Gale M Jr. Regulation of innate immunity against hepatitis C virus infection. Hepatol Res. 2008 ; 38(2) : 115 - 122.
21. Saito T, Gale M Jr. Differential recognition of double-stranded RNA by RIG-I-like receptors in antiviral immunity. J Exp Med. 2008 ; 205(7) : 1523-7.
22. Gale M Jr, Foy EM. Evasion of intracellular host defence by hepatitis C virus. Nature. 2005 ; 436(7053) : 939-45.
23. Loo YM, Owen DM, Li K, et al.Viral and therapeutic control of IFN-beta promoter stimulator 1 during hepatitis C virus infection. Proc Natl Acad Sci U S A. 2006 ; 103(15): 6001-6.

24. Chan CH, Hadlock KG, Foung SK et al. 1-69 gene is preferentially used by hepatitis C virus-associated B cell lymphomas and by normal B cells responding to the E2 viral antigen. Blood, 2002 ; 97 : 1023 - 1026.
25. Yap KL, Ada GL and McKenzie IFC. Transfer of specific cytotoxic T lymphocytes protects mice inoculated with influenza virus. Nature 1978 ; 273 (5659) : 238–239.
26. Zinkernagel RM, Haenseler E, Leist T, et al. T cell-mediated hepatitis in mice infected with lymphocytic choriomeningitis virus. Liver cell destruction by H-2 class I-restricted virus-specific cytotoxic T cells as a physiological correlate of the 51Cr-release assay? Journal of Experimental Medicine, 1986 ; 164(4) : 1075–1092.
27. Banchereau J and Steinman RM. Dendritic cells and the control of immunity. Nature, 1998 ; 392 (6673) : 245–252.
28. Chan SH, Perussia B, Gupta JW et al. Induction of interferon gamma production by natural killer cell stimulatory factor: characterization of the responder cells and synergy with other inducers. J Exp Med., 1991 ; 173(4) : 869 - 879.
29. Heufler C, Koch F, Stanzl U et al. Interleukin-12 is produced by dendritic cells and mediates T helper 1 development as well as interferon-gamma production by T helper 1 cells. Eur J Immunol, 1996 ; 26(3) : 659 - 668.
30. Kägi D, Vignaux F, Ledermann B, et al. Fas and perforin pathways as major mechanisms of T cell-mediated cytotoxicity. Science 1994 ; 265 (5171) : 528–530.
31. Kojima H, Shinohara N, Hanaoka S, et al. Two distinct pathways of specific killing revealed by perforin mutant cytotoxic T lymphocytes. Immunity 1994 ; 1(5) : 357–364.
32. Samuel CE. Antiviral actions of interferons. Clinical Microbiology Reviews 2001 ; 14 (4) : 778–809.
33. Liu YJ, Kanzler H, Soumelis V and Gilliet M. Dendritic cell lineage, plasticity and cross-regulation. Nature Immunology 2001 ; 2(7) : 585–589.
34. Watarai H, Sekine E, Inoue S, et al. PDC-TREM, a plasmacytoid dendritic cell-specific receptor, is responsible for augmented production of type I interferon. Proceedings of the National Academy of Sciences of the United States of America 2008 ; 105(8) : 2993–2998.
35. Pape GR, Gerlach TJ, Diepolder HM et al. Role of the specific T-cell response for clearance and control of hepatitis C virus. J Viral Hepat., 1999 ; 6 : 36 - 40.
36. Aberle JH, Formann E, Steindl-Munda P et al. Prospective study of viral clearance and CD4(+) T-cell response in acute hepatitis C primary infection and reinfection. J Clin Virol., 2006 ; 36(1) : 24 - 31.
37. Valiante NM, D'Andrea A, Crotta S et al. Life, activation and death of intrahepatic lymphocytes in chronic hepatitis C. Immunol. Rev., 2000 ; 174 : 77 – 89.
38. Su AI, Pezacki JP, Wodicka L et al. Genomic analysis of the host response to hepatitis C virus infection. Proc. Natl. Acad. Sci. USA, 2002 ; 99 : 15669-15674.
39. Koziel MJ. The role of immune responses in the pathogenesis of hepatitis C virus infection. J. Viral Hepat., 1997 ; 4 : 31 – 41.
40. Chisari FV. Cytotoxic T cells and viral hepatitis. J. Clin. Invest., 1997 ; 99 : 1472 -1477.
41. Sarobe P, Lasarte JJ, Zabaleta A et al. Hepatitis C virus structural proteins impair dendritic cell maturation and inhibit in vivo induction of cellular immune responses. J Virol, 2003 ; 77(20) : 10862 - 10871.
42. Szabo G and Dolganiuc A. Subversion of plasmacytoid and myeloid dendritic cell functions in chronic HCV infection. Immunobiology 2005 ; 210(2–4) : 237–247.
43. Lozach PY, Lortat-Jacob H, De Lacroix DL et al. DC-SIGN and L-SIGN are high-affinity binding receptors for hepatitis C virus glycoprotein E2. J. Biol. Chem., 2003 ; 278 : 20358 - 20366.
44. Pöhlmann S, Zhang J, Baribaud F, et al. Hepatitis C virus glycoproteins interact with DC-SIGN and DC-SIGNR. Journal of Virology 2003 ; 77 (7) : 4070–4080.
45. Irshad M, I Khushboo, Singh Shiwani et al. Hepatitis C Virus (HCV) : Review of Immunological Aspects. Inter Rev Immunol, 2008 ; 27 : 497 - 517.
46. Weiner AJ, Brauer MJ, Rosenblatt J et al. Variable and hypervariable domains are found in the regions of HCV corresponding to the flavivirus envelope and NS1 proteins and the pestivirus envelope glycoproteins. Virol, 1991 ; 180(2) : 842 - 848.
47. Farci P, Shimoda A, Coiana A et al. The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. Science, 2000 ; 288(5464) : 339 - 344.
48. Farci P, Alter HJ, Wong DC et al. Prevention of hepatitis C virus infection in chimpanzees after antibody-mediated in vitro neutralization. Proc Natl Acad Sci USA, 1994 ; 91(16) : 7792 – 7796.
49. Shimizu YK, Hijikata M, Iwamoto A et al. Neutralizing antibodies against hepatitis C virus and the emergence of neutralization escape mutant viruses. J. Virol., 1994 ; 68 : 1494 - 1500.
50. Del Porto P, Puntoriero G, Scottà C et al. High prevalence of hypervariable region 1-specific and -cross-reactive CD4(+) T cells in HCV-infected individuals responsive to IFN-alpha treatment. Virol, 2000 ; 269(2) : 313 - 324.
51. Tsai SL, Chen YM, Chen MH et al. Hepatitis C virus variants circumventing cytotoxic T lymphocyte activity as a mechanism of chronicity. Gastroenterol, 1998 ; 115(4) : 954 - 965.
52. Frasca L, Scottà C, Del Porto P et al. Antibody-selected mimics of hepatitis C virus hypervariable region 1 activate both primary and memory Th lymphocytes. Hepatol, 2003 ; 38(3) : 653 - 663.
53. Grakoui A, Shoukry NH, Woollard DJ, et al. HCV persistence and immune evasion in the absence of memory T cell help. Science, 2003 ; 302(5645) : 659 - 662.
54. Manzin A, Solforosi L, Petrelli E et al. Evolution of hypervariable region 1 of hepatitis C virus in primary infection. J. Virol., 1998 ; 72(7) : 6271 - 6276.
55. Ray SC, Wang YM, Laeyendecker O et al. Acute hepatitis C virus structural gene sequences as predictors of persistent viremia: hypervariable region 1 as a decoy. J. Virol., 1999 ; 73(4) : 2938 - 2946.
56. Dustin LB, Rice CM. Flying under the radar: the immunobiology of hepatitis C. Annu. Rev. Immunol., 2007 ; 25 : 71 - 99.
57. Shoukry NH, Cawthon AG, Walker CM. Cell-mediated immunity and the outcome of hepatitis C virus infection. Annu. Rev. Microbiol., 2004; 58: 391-424.
58. Bowen DG, Walker CM. Adaptive immune responses in acute and chronic hepatitis C virus infection. Nature, 2005 ; 436 : 946 – 952.

59. Sugimoto K, Ikeda F, Stadanlick J et al. Suppression of HCV-specific T cells without differential hierarchy demonstrated ex vivo in persistent HCV infection. Hepatol, 2003 ; 38 : 1437 – 1448.
60. Rushbrook SM, Ward SM, Unitt E et al. Regulatory T cells suppress in vitro proliferation of virus-specific CD8+ T cells during persistent hepatitis C virus infection. J. Virol., 2005 ; 79 : 7852 - 7859.
61. Ward SM, Fox BC, Brown PJ et al. Quantification and localisation of FOXP3+ T lymphocytes and relation to hepatic inflammation during chronic HCV infection. J. Hepatol., 2007 ; 47 : 316 – 324.
62. Thimme R, Lohmann V, Weber F. A target on the move: innate and adaptive immune escape strategies of hepatitis C virus. Antiviral Res., 2006 ; 69 : 129 – 141.
63. Boettler T, Spangenberg HC, Neumann-Haefelin C et al. T cells with a CD4+CD25+ regulatory phenotype suppress in vitro proliferation of virus-specific CD8+ T cells during chronic hepatitis C virus infection. J. Virol., 2005 ; 79 : 7860 – 7867.
64. Cabrera R, Tu Z, Xu Y et al. An immunomodulatory role for CD4(+)CD25(+) regulatory T lymphocytes in hepatitis C virus infection. Hepatol, 2004 ; 40 : 1062 – 1071.
65. Bolacchi F, Sinistro A, Ciaprini C et al. Increased hepatitis C virus (HCV)-specific CD4+CD25+ regulatory T lymphocytes and reduced HCV-specific CD4+ T cell response in HCV-infected patients with normal versus abnormal alanine aminotransferase levels. Clin. Exp. Immunol., 2006 ; 144 : 188 – 196.
66. Manigold T, Shin EC, Mizukoshi E et al. Foxp3+CD4+CD25+ T cells control virus-specific memory T cells in chimpanzees that recovered from hepatitis C. Blood, 2006 ; 107 : 4424 – 4432.
67. MacDonald AJ, Duffy M, Brady MT et al. CD4 T helper type 1 and regulatory T cells induced against the same epitopes on the core protein in hepatitis C virus-infected persons. J. Infect. Dis., 2002 ; 185 : 720 -727.
68. Clément S, Pascarella S, Negro F. Hepatitis C Virus Infection: Molecular Pathways to Steatosis, Insulin Resistance and Oxidative Stress. Viruses, 2009, 1 : 126-143.
69. Bertram Bengsch, Bianca Seigel, Marianne Ruhl et al. Coexpression of PD-1, 2B4, CD160 and LRG1 on Exhausted HCV-Specific CD8+ T Cells Is Linked to Antigen Recognition and T Cell Differentiation. PLoS Pathog. 2010 ; 6 (6) : e1000947.
70. Radziewicz H, Ibegbu CC, Fernandez ML et al. Liver-infiltrating lymphocytes in chronic human hepatitis C virus infection display an exhausted phenotype with high levels of PD-1 and low levels of CD127 expression. J Virol. 2007 ; 81: 2545–2553.
71. Fujita N, Sugimoto R, Ma N et al. Comparison of hepatic oxidative DNA damage in patients with chronic hepatitis B and C. J. Viral Hepat., 2008 ; 15 : 498-507.
72. Romero MJ, Bosch-Morell F, Romero B et al. Serum malondialdehyde: possible use for the clinical management of chronic hepatitis C patients. Free Radic. Biol. Med., 1998 ; 25, 993-997.
73. Mitsuyoshi H, Itoh Y, Sumida Y et al. Evidence of oxidative stress as a cofactor in the development of insulin resistance in patients with chronic hepatitis C. Hepatol. Res., 2008 ; 38 : 348-353.
74. Houglum K, Venkataramani A, Lyche K et al. A pilot study of the effects of d-alphatocopherol on hepatic stellate cell activation in chronic hepatitis C. Gastroenterol, 1997 ; 113 : 1069-1073.
75. Gabbay E, Zigmond E, Pappo O et al. Antioxidant therapy for chronic hepatitis C after failure of interferon: results of phase II randomized, double-blind placebo controlled clinical trial. World J. Gastroenterol., 2007 ; 13 : 5317-5323.
76. Okuda M, Li K, Beard MR et al. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterol, 2002 ; 122 : 366-375.
77. Abdalla MY, Ahmad IM, Spitz DR et al. Hepatitis C virus-core and non structural proteins lead to different effects on cellular antioxidant defenses. J. Med. Virol., 2005 : 76, 489-497.
78. Dionisio N, Garcia-Mediavilla MV, Sanchez-Campos S et al. Hepatitis C virus NS5A and core proteins induce oxidative stress-mediated calcium signalling alterations in hepatocytes. J. Hepatol., 2009 ; 50 : 872-882.
79. Korenaga M, Wang T, Li Y et al. Hepatitis C virus core protein inhibits mitochondrial electron transport and increases reactive oxygen species (ROS) production. J. Biol. Chem., 2005 ; 280 : 37481-37488.
80. Li Y, Boehning DF, Qian T et al. Hepatitis C virus core protein increases mitochondrial ROS production by stimulation of Ca2+ uniporter activity. Faseb J., 2007 ; 21 : 2474-2485.
81. Machida K, Cheng KT, Lai CK et al. Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. J. Virol., 2006 ; 80 : 7199-7207.
82. Miyanari Y, Atsuzawa K, Usuda N et al. The lipid droplet is an important organelle for hepatitis C virus production. Nat. Cell Biol., 2007 ; 9 : 1089-1097.
83. Gong G, Waris G, Tanveer R et al. Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-kappa B. Proc. Natl. Acad. Sci. USA. 2001 ; 98 : 9599-9604.
84. Joyce MA, Walters KA, Lamb SE et al. HCV induces oxidative and ER stress, and sensitizes infected cells to apoptosis in SCID/Alb-uPA mice. PLoS Pathog., 2009 ; 5 : 1000291.
85. Thoren F, Romero A, Lindh M et al. A hepatitis C virus-encoded, nonstructural protein (NS3) triggers dysfunction and apoptosis in lymphocytes: role of NADPH oxidase-derived oxygen radicals. J. Leukoc. Biol., 2004 ; 76 : 1180-1186.
86. Asselah T, Rubbia-Brandt L, Marcellin P et al. Steatosis in chronic hepatitis C: why does it really matter? Gut, 2006 ; 55 : 123-130.
87. Khan M, Jahan S, Khaliq S et al. Interaction of the hepatitis C virus (HCV) core with cellular genes in the development of HCV-induced steatosis. Arch Virol. 2010 ;155 :1735-53.
88. Hwang SJ, Lee SD. Hepatic steatosis and hepatitis C: Still unhappy bedfellows? J Gastroenterol Hepatol. 2011 ; 26 : 96-101.
89. Rubbia-Brandt L, Giostra E, Mentha G et al. Expression of liver steatosis in hepatitis C virus infection and pattern of response to alpha-interferon. J. Hepatol., 2001 ; 35 : 307.
90. Barba G, Harper F, Harada T et al. Hepatitis C virus core protein shows a cytoplasmic localization and associates to cellular lipid storage droplets. Proc. Natl. Acad. Sci. USA, 1997 ; 94 : 1200-1205.
91. Moriya K, Yotsuyanagi H, Shintani Y et al. Hepatitis C virus core protein induces hepatic steatosis in transgenic mice. J. Gen.Virol., 1997 ; 78 : 1527-1531.

92. Rubbia-Brandt L, Fabris P, Paganin S et al. Steatosis affects chronic hepatitis C progression in a genotype specific way. Gut, 2004 ; *53 :* 406-412.
93. Adinolfi LE, Gambardella M, Andreana A et al. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatol, 2001 ; 33 : 1358-1364.
94. Hui JM, Kench J, Farrell GC et al. Genotype-specific mechanisms for hepatic steatosis in chronic hepatitis C infection. J. Gastroenterol. Hepatol., 2002 ; 17 : 873-881.
95. Abid K, Pazienza V, de Gottardi A et al. An in vitro model of hepatitis C virus genotype 3a-associated triglycerides accumulation. J. Hepatol., 2005 ; 42 : 744-751.
96. Rubbia-Brandt L, Quadri R, Abid K et al. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. J Hepatol, 2000 ; 33 : 106-115.
97. Fujie H, Yotsuyanagi H, Moriya K et al. Steatosis and intrahepatic hepatitis C virus in chronic hepatitis. J. Med. Virol., 1999 ; 59 : 141-145.
98. Kumar D, Farrell GC, Fung C et al. Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response. Hepatol, 2002 ; 36 : 1266-1272.
99. Poynard T, Ratziu V, McHutchison J et al. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. Hepatol, 2003 ; 38 : 75-85.
100.Hofer H, Bankl HC, Wrba F et al. Hepatocellular fat accumulation and low serum cholesterol in patients infected with HCV-3a. Am. J. Gastroenterol., 2002 ; 97 : 2880-2885.
101.Oem JK, Jackel-Cram C, Li YP et al. Activation of sterol regulatory element-binding protein 1c and fatty acid synthase transcription by hepatitis C virus non-structural protein 2. J. Gen. Virol., 2008 ; 89: 1225-1230.
102.Shi ST, Polyak SJ, Tu H et al. Hepatitis C virus NS5A colocalizes with the core protein on lipid droplets and interacts with apolipoproteins. Virol, 2002 ; 292 : 198-210.
103.Serfaty L, Andreani T, Giral P et al. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. J. Hepatol., 2001 ; 34 : 428-434.
104.Perlemuter G, Sabile A, Letteron P et al. Hepatitis C virus core protein inhibits microsomal triglyceride transfer protein activity and very low density lipoprotein secretion: a model of viralrelated steatosis. Faseb J., 2002 ; 16 : 185-194.
105.Park CY, Jun HJ, Wakita T et al. Hepatitis C virus nonstructural 4B protein modulates sterol regulatory element-binding protein signaling via the AKT pathway. J. Biol. Chem., 2009 ; 284 : 9237-9246.
106.Jackel-Cram C, Babiuk LA, Liu Q. Up-regulation of fatty acid synthase promoter by hepatitis C virus core protein: genotype-3a core has a stronger effect than genotype-1b core. J. Hepatol., 2007 ; 46 : 999-1008.
107.Tsutsumi T, Suzuki T, Shimoike T et al. Interaction of hepatitis C virus core protein with retinoid X receptor alpha modulates its transcriptional activity. Hepatol, 2002 ; 35 : 937-946.
108.Cheng Y, Dharancy S, Malapel M et al. Hepatitis C virus infection down-regulates the expression of peroxisome proliferator-activated receptor alpha and carnitine palmitoyl acyl-CoA transferase 1A. World J. Gastroenterol., 2005 ; 11 : 7591-7596.
109.de Gottardi A, Pazienza V, Pugnale P et al. Peroxisome proliferator-activated receptor-alpha and –gamma mRNA levels are reduced in chronic hepatitis C with steatosis and genotype 3 infection. Aliment Pharmacol. Ther., 2006 ; 23 : 107-114.
110.Dharancy S, Malapel M, Perlemuter G et al. Impaired expression of the peroxisome proliferator-activated receptor alpha during hepatitis C virus infection. Gastroenterol, 2005 ; 128 : 334-342.
111.Pazienza V, Clément S, Pugnale P et al. The hepatitis C virus core protein of genotypes 3a and 1b down regulates insulin receptor substrate 1 through genotype-specific mechanisms. Hepatol, 2007 ; 45(5) : 1164- 1171.
112.Arrese M, Riquelme A, Soza A. Insulin resistance, hepatic steatosis and hepatitis C: a complex relationship with relevant clinical implications.. Ann Hepatol. 2010 ; 9 :112-8.
113.Fartoux L, Poujol-Robert A, Guechot J et al. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. Gut, 2005 ; 54 : 1003-1008.
114.Bieche I, Asselah T, Laurendeau I et al. Molecular profiling of early stage liver fibrosis in patients with chronic hepatitis C virus infection. Virol, 2005 ; 332 : 130-144.
115.Foster DA. Regulation of mTOR by phosphatidic acid? *Cancer Res.*, 2007 ; *67 :* 1-4.
116.Holland WL, Summers SA. Sphingolipids, insulin resistance, and metabolic disease: new insights from in vivo manipulation of sphingolipid metabolism. Endocr. Rev., 2008 ; 29 : 381-402.
117.Shintani Y, Fujie H, Miyoshi H et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterol, 2004 ; 126 : 840-848.
118.Kawaguchi T, Yoshida T, Harada M et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. Am. J. Pathol., 2004 ; 165 : 1499-1508.
119.Bernsmeier C, Duong FH, Christen V et al. Virus-induced over-expression of protein phosphatase 2A inhibits insulin signalling in chronic hepatitis C. J. Hepatol., 2008 ; 49 : 429-440.
120.Banerjee S, Saito K, Ait-Goughoulte M et al. Hepatitis C virus core protein upregulates serine phosphorylation of insulin receptor substrate-1 and impairs the downstream akt/protein kinase B signaling pathway for insulin resistance. J. Virol., 2008 ; 82 : 2606-2612.
121.Conjeevaram HS, Kleiner DE, Everhart JE et al. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. Hepatol, 2007 ; 45 : 80-87.
122.Walsh MJ, Jonsson JR, Richardson MM et al. Non-response to antiviral therapy is associated with obesity and increased hepatic expression of suppressor of cytokine signalling 3 (SOCS-3) in patients with chronic hepatitis C, viral genotype 1. Gut, 2006 ; 55 : 529-535.
20.