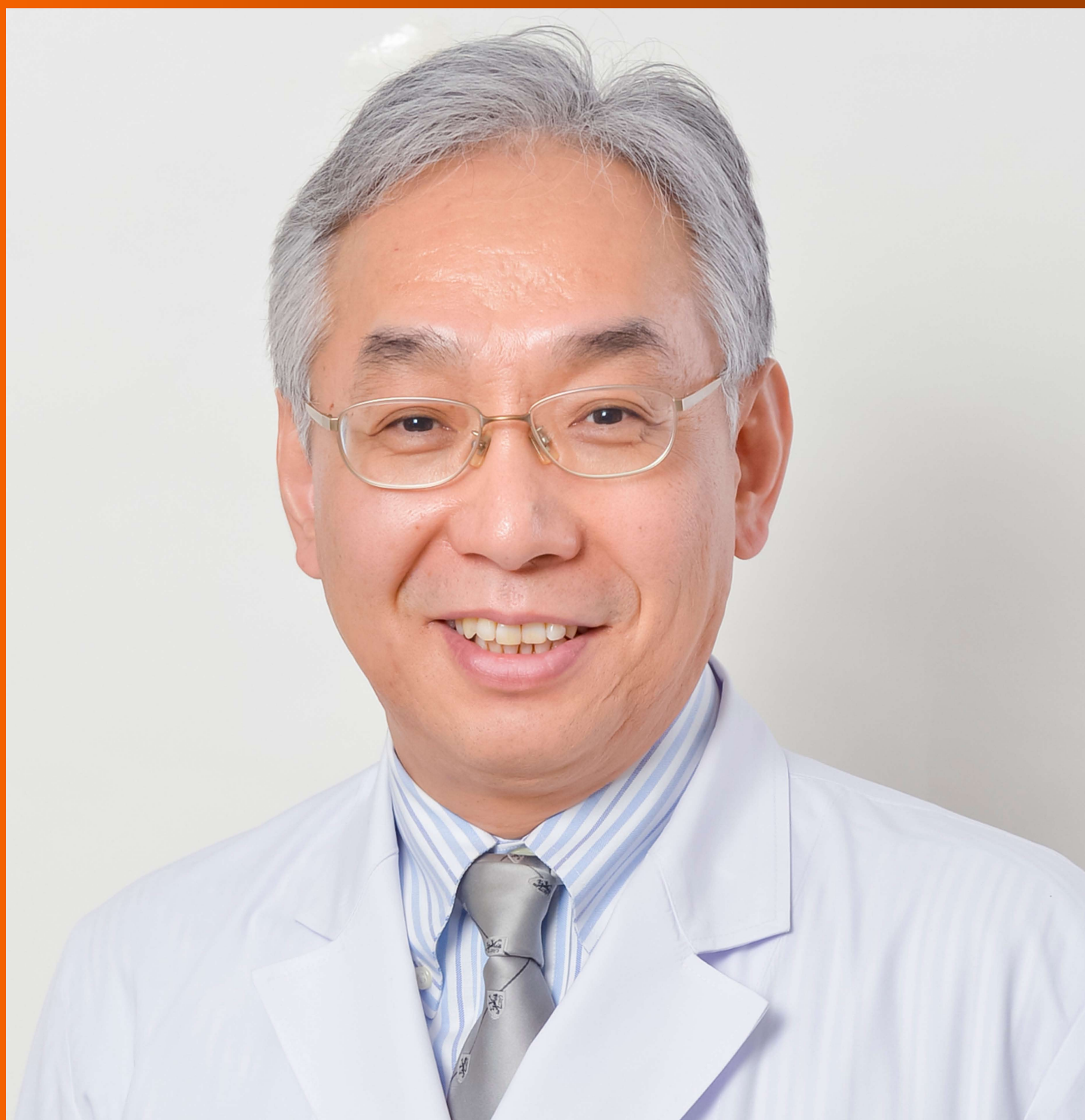


World Journal of *Hepatology*

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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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World Journal of Hepatology is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, and Scopus.

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I-IV Editorial Board

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NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

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Pleasanton, CA 94588, USA
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Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE
December 28, 2017

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INSTRUCTIONS TO AUTHORS
<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
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Molecular basis of hepatocellular carcinoma induced by hepatitis C virus infection

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Author contributions: All authors made equal contribution in the preparation of this manuscript and final approval of the version of it to be published.

Conflict-of-interest statement: The authors declare here that there is no conflict of interest related to this study among them.

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Manuscript source: Invited manuscript

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Received: October 9, 2017

Peer-review started: October 10, 2017

First decision: November 7, 2017

Revised: November 8, 2017

Accepted: December 5, 2017

Article in press: December 6, 2017

Published online: December 28, 2017

Abstract

Present study outlines a comprehensive view of published information about the underlying mechanisms operational for progression of chronic hepatitis C virus (HCV) infection to development of hepatocellular carcinoma (HCC). These reports are based on the results of animal experiments and human based studies. Although, the exact delineated mechanism is not yet established, there are evidences available to emphasize the involvement of HCV induced chronic inflammation, oxidative stress, insulin resistance, endoplasmic reticulum stress, hepato steatosis and liver fibrosis in the progression of HCV chronic disease to HCC. Persistent infection with replicating HCV not only initiates several liver alterations but also creates an environment for development of liver cancer. Various studies have reported that HCV acts both directly as well as indirectly in promoting this process. Whereas HCV related proteins, like HCV core, E1, E2, NS3 and NS5A, modulate signal pathways dysregulating cell cycle and cell metabolism, the chronic infection produces similar changes in an indirect way. HCV is an RNA virus and does not integrate with host genome and therefore, HCV induced hepatocarcinogenesis pursues a totally different mechanism causing imbalance between suppressors and proto-oncogenes and genomic integrity. However, the exact mechanism of HCC inducement still needs a full understanding of various steps involved in this process.

Key words: Hepatitis C virus; Hepatocellular carcinoma; Fibrosis; Core; NS5A; Inflammation

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Core tip: Hepatocellular carcinoma (HCC) is one of the most common cancer occurring in human population all over the world. Chronic hepatitis C virus (HCV) infection is considered as a major cause of producing

HCC in developed countries. HCV infection induces chronic inflammation in liver, which initiates several changes including production of oxidative stress, steatosis, progressive fibrosis, cirrhosis and finally HCC. HCV related proteins also interact directly with cellular proteins at various steps of cell signaling disturbing cell cycle and regeneration process. HCC is supposed, now a days, to be the foremost indication for liver transplant.

Irshad M, Gupta P, Irshad K. Molecular basis of hepatocellular carcinoma induced by hepatitis C virus infection. *World J Hepatol* 2017; 9(36): 1305-1314 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i36/1305.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i36.1305>

INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem reported from all parts of the world. HCV was characterised by Choo *et al.*^[1] and Kuo *et al.*^[2] in 1989. As per World Health Organization report, about 3% world population is having HCV infection with 170 million people becoming as chronic carriers of HCV^[3]. These people always remain at high risk of developing cirrhosis of liver and hepatocellular carcinoma (HCC) in later years. There is an increase in the cases of HCC with 1%-7% chronic HCV infected patients developing HCC after establishment of cirrhosis^[4,5]. HCC caused by HCV infection is a prominent indication for liver transplant^[6].

HCV is an enveloped RNA virus included under Flaviviridae family^[7]. It has 9.6 kb single stranded RNA with positive polarity. HCV genome encodes a long protein of 3000 amino acids which undergoes proteolysis to yield structural proteins (Envelop E1, E2 and Core) and nonstructural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B)^[8]. Whereas structural proteins play important role in its morphological features and entry into the host cell, nonstructural proteins are involved mainly in viral replication, assembly and pathogenesis of diseases caused. HCV genome is highly heterogeneous with 32%-35% variations in different HCV genotypes^[9]. Based on current reports at least seven genotypes and several subtypes of HCV have been reported till date^[10]. Although, variability of genomic sequence has been reported throughout the viral genome, the E1 and E2 regions have been reported to be maximally variable^[10].

HCC develops more frequently in cirrhotic patients in comparison to those having mild fibrosis^[11]. In addition, hepatitis B virus infection, insulin resistance, obesity and steatohepatitis also promote HCV related HCC^[12]. HCC may result from a combined effect of host, environment and viral factors^[13]. Immune mediated chronic inflammation during HCV infection is supposed to facilitate the development of HCC. Simultaneously, it may induce HCC by altering many cell pathways involved in cell proliferation, energy metabolism, and

apoptosis^[14].

As such, HCV is a non-cytopathic virus and initiates hepatic injury by immune mediated reaction-cascade. Although, it is not fully established, however, on the basis of animal experiments and human studies, it is assumed that HCV plays both direct as well as indirect role in inducing HCC^[15,16]. Current literature demonstrates that cell death, regeneration, inflammation, oxidative stress and steatosis noted during chronic HCV infection are some of the main reasons responsible for hepatocarcinogenesis^[13,17]. Similarly, dysregulation of cell cycle by altered intracellular signaling cascade arising during chronic HCV infection is an important phenomenon in the direction of HCC development. In fact, mechanism of hepatocarcinogenesis during chronic HCV infection is slightly distinct from those responsible for causing other types of cancers. HCV core protein was found to induce HCC in absence of genetic aberrations and so, this was named as "non- Vogelstein- type" carcinogenesis in some reports^[18]. This may explain a high incidence and multicentric nature of HCC developed during HCV infection. Present review describes a compilation of informations on the mechanisms of HCC development during chronic hepatitis C virus (HCV) infection.

MECHANISMS OF HCV INDUCED HCC

HCV is a hepatotropic virus and enters host cell *via* a complex sets of molecules present on cell surface including CD81 (receptor molecule), SRB-1 (scavenger receptor) and Occludin-1 and Claudin (tight junction proteins)^[19-21]. After its entry, HCV replicates in hepatocytes and leads to different types of cellular and immune mediated changes. A majority of patients infected with HCV fail to clear the virus. In these patients HCV persists for longer duration causing chronic HCV infection and a high risk for progressive hepatic fibrosis, cirrhosis and HCC^[22]. Simultaneously, the ensuing chronic inflammation associated with oxidative stress and emerging cellular DNA damage, also contribute to development of HCV associated HCC. The question whether cancer develops in infected hepatocytes or in uninfected hepatocytes still needs to be answered. Based on some experimental studies it was reported that Ki67 proliferation marker is raised in advanced HCV infected hepatocytes pointing towards HCV infected cells at higher risk for HCC as compared to uninfected cells^[23,24]. Several studies suggest that liver cancer develops by an interplay of host, viral and environmental factors. All these finally bring some epigenetic changes in HCV infected hepatocytes leading to development of HCC^[13,25].

Chronic HCV infection is often accompanied by several disturbances including inflammation, steatosis and progressive fibrosis in the liver^[25]. All these changes ultimately progress to cirrhosis and hepatocarcinogenesis. Therefore, it is suggested that HCC is caused by an interplay of chronic inflammation, insulin resistance

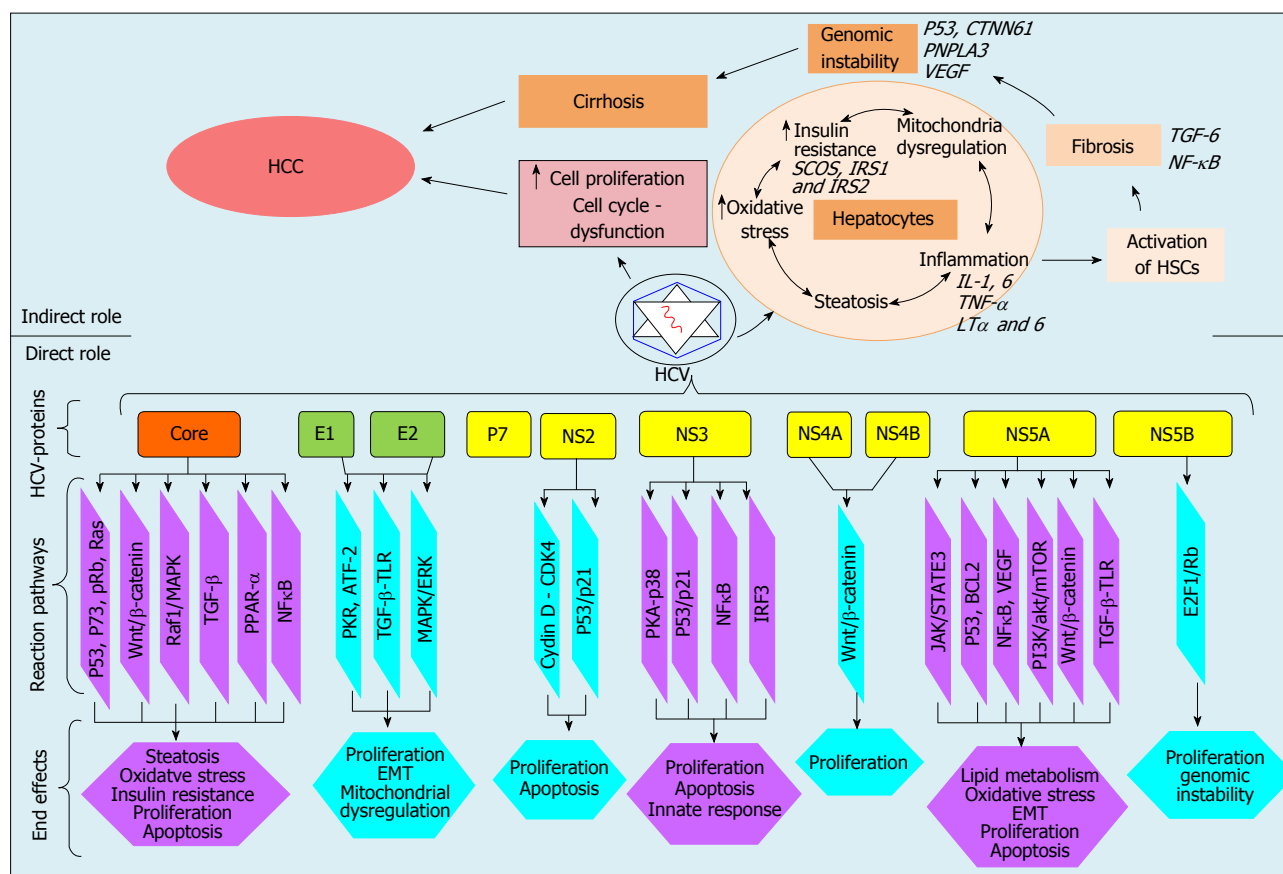


Figure 1 Direct and indirect role of hepatitis C virus in causing hepatocellular carcinoma. Role of hepatitis C virus (HCV) and its structural and non-structural proteins in inducement of hepatocellular carcinoma (HCC) during chronic HCV infection. Viral onset causes various cellular alterations leading to activation of hepatic stellate cells which in turn, produce progressive fibrosis leading to cirrhosis of liver. Simultaneously, HCV also dysregulates cell cycle causing cell proliferation. Both cirrhosis and cell proliferation induce development of HCC. In this figure, the top half portion shows an indirect role of HCV via cellular alterations and causing cirrhosis by inter-related mechanisms and cell dysregulation leading to cell proliferation. The lower half shows a direct role of HCV by interaction of its proteins with various cellular pathways producing different effects as preconditions for inducement of HCC. The link bars show the underlying pathways and the bottom boxes show the end effects. EMT: Epithelial to mesenchymal trans-differentiation; HSCs: Hepatic stellate cells; TGF: Transforming growth factor; PKR: Protein kinase; VEGF: Vascular endothelial growth factor; TNF- α : Tumor necrosis factor- α ; PPAR- α : Peroxisome proliferator-activated receptor alpha; ERK: Extracellular signal regulated protein kinase; PKA: Protein kinase A; NF- κ B: Nuclear factor- κ B.

(IR), hepatosteatosis, oxidative stress, fibrosis, and the resulting liver damages by chronic HCV infection. This interplay produces a pro-oncogenic microenvironment which promotes fibrogenesis and genetic instability^[26]. Simultaneous with a direct transforming role of HCV, the liver microenvironment is supposed to have a modulating effect on cell transforming process during HCC development. Several HCV proteins have direct oncogenic effects and use liver changes in upregulating mitogenic process^[27]. At the same time, increasing cell proliferation in this environment also results in DNA damage causing genomic disturbances. This becomes another basis for malignant transformation of hepatocytes. In view of all these available reports^[25-27], the mechanism of HCV induced HCC may be illustrated by a direct and indirect role of HCV in relation to the microenvironment produced by chronic HCV infection (Figure 1).

HOST FACTORS

Inflammation and oxidative stress in HCV induced HCC

Immune mediated inflammation caused during chronic

HCV infection indirectly triggers hepatocarcinogenesis. Simultaneous with a direct role of HCV in inducement of HCC by altering several cellular pathways involved in metabolism, DNA repair and apoptosis^[14], chronic HCV infection enhances the reactive oxygen species (ROS) which damages the liver cells. At the same time, HCV also induces inflammation by activating hepatic stellate cells (HSCs)^[28]. These HSCs get activated by ROS, growth factors, cytokines, adipokines and chemokines secreted by hepatocytes, Kuffer cells and inflammatory cells^[29]. The progress of disease is increased by cumulative effect of inflammation, ROS, steatosis and IR caused during chronic HCV infection. The activated HSCs, under the effect of fibrogenic cytokines undergo epithelial to mesenchymal trans-differentiation (EMT) into myofibroblast like cells which cause liver fibrosis^[14]. Transforming growth factor beta (TGF- β) cytokine regulates EMT demonstrating its pro-oncogenic functions^[30]. Hepatic fibrosis is closely associated with HCC development. EMT pathway plays a major role in transition of hepatocyte to cancerous cell and process of metastasis known with expression of E-cadherin and

Vimentin^[31]. The IR stimulates HSCs and links fibrosis with steatosis. The process of fibrogenesis is regulated by a number of signaling pathways including SMADs, phosphatidylinositol 3-kinases (PI3K), protein kinase (Akt), mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinases (JNKs) pathways. JNK activation by IL1- β cytokine increases fibrogenesis, oncogenesis and cell motility^[32,33]. Thus all these liver alterations finally produce a suitable environment for development of HCC in chronic HCV infection.

Insulin resistance and hepato steatosis in HCV induced HCC

It has been observed that HCV *genotype-3* induces steatosis in patients with chronic HCV infection^[34]. HCV induces steatosis by increasing lipid synthesis and reducing its secretion and degradation. The structural and nonstructural proteins of HCV directly interfere in lipid synthesis^[35] and very-low-density lipoprotein secretion^[36,37]. These HCV related proteins also inhibit fatty acid oxidation^[38,39] and enhance fatty acid release from adipocytes^[34]. All this finally results in hepatic steatosis. The HCV related proteins are also involved in producing ROS^[40] and glucose homeostasis. HCV interferes with insulin signaling by proteosomal degradation of insulin receptor substrate 1 (IRS-1) and IRS-2 by suppressor of cytokine signaling (SOCS) protein or PI3K/Akt/mTOR pathway. IRS-1 is reported to be inactivated by TGF- α and PI3K/Akt also^[41]. In this manner, the early stage of chronic HCV infection with increasing steatosis and IR creates an environment to help in hepatocarcinogenesis leading to development of HCC.

Immune mediated liver alteration in HCV induced HCC

HCV influences both innate and adaptive immunity. This virus inhibits type 1 Interferon production and CD4⁺ T-cell transformation to Th2, Th17 and regulatory T-cell. This disturbs the function of cytotoxic CD8⁺ T-cells and natural killer (NK) cells^[42-48]. It results in chronic liver inflammation which disturbs tissue homeostasis and promotes pro-carcinogenic environment. Simultaneously, there is an increase in the release of ROS, nitric oxide (NO), cytotoxic cytokines and lipid peroxidation. It also helps in immune escape of neoplastic transformed cells facilitating the development of HCC^[49]. During chronic HCV infection, the inflammatory cytokine like tumor necrosis factor- α (TNF- α), interleukin (IL)-1, IL-23, IL-6 and lymphotoxins-alpha and beta (LT- α and β) are also increased causing chronic liver inflammation and HCC progression^[49-51]. There is already a report demonstrating an important role of LT- α and LT- β in the development of HCC^[51]. In fact, activation of NF- κ B pathway by LTs triggers the hepatocarcinogenesis by increasing production of chemokines and cytokines. In patients with chronic HCV infection, the liver infiltrating T and B-cells not only fail viral clearances but also increase chronic inflammation^[51,52]. Also, an increased number of CD8⁺ is accompanied by reduction in NK and NKT cells which

are involved in cancer immune surveillance^[52]. These informations indicate that during chronic HCV infection there is a regular tumor promoting inflammation and impaired anticancer immune scanning, which ultimately facilitates towards HCC.

Hepatic fibrosis in HCV induced HCC

As described earlier there is high occurrence of steato-hepatitis in patients with chronic HCV infection. The accumulation of free fatty acid induces production of ROS and mitochondrial dysfunction and Endoplasmic reticulum (ER) stress. In turn, oxidative stress stimulates lipid peroxidation and increases inflammation in liver tissue. Increased ROS levels have direct effect on fibrosis by increasing collagen 1 expression^[50]. The HCV induced steatosis changes the liver T-cell function. HCV related proteins in the liver develop extensive steatosis which is accompanied by an infiltrate of CD8⁺ T-cell secreting Th2 type cytokine^[53]. A massive liver infiltration by CD8⁺ and NKT cells induces steatosis, inflammation and carcinogenesis^[54]. In HCV infected patients, the risk of HCC development may also be linked with the severity of liver fibrosis. TGF- β is an important cytokine involved in fibrogenesis. Its expression is directly affected by HCV related proteins or oxidative/ER stress and NF- κ B pathway activation^[55-58]. This concludes that hepatic fibrosis caused by various mechanisms is a big inducer promoting hepatocarcinogenesis.

Genetic factors in HCV induced HCC

There are a number of genes associated with HCV induced HCC. The tumor suppressor gene *P53* was the first one noted for its association with development of HCC. Recent studies have shown a subset of genes frequently mutated in HCV patients^[59,60]. Oncogene CTNNB1 which encodes β -catenin protein of WNT-pathway shows a mutation of 30%. WNT ligands activate signal transduction cascade resulting in inhibition of β -catenin degradation complex. It has been observed that WNT pathway gets mutated in HCC, which stabilizes β -catenin. This β -catenin translocates to the nucleus and regulates genes responsible for cell survival and proliferation. NS5A indirectly regulates the WNT pathway through PI3K and activate Akt. Increased β -catenin has been observed in HCV infected cells. The significance of β -catenin with in HCV infected cells is still uncertain^[61]. However, its level is increased mostly in HCC patients. Similarly, reduction in the size of telomere triggers cellular senescence. Activation mutation in the telomerase reverse transcriptase (TERT) promoter gene has been detected in HCC induced by HCV infection in addition to other etiologies^[62-64]. HCV core protein downregulates CDKN2A expression to overcome hepatocyte senescence. Increased telomerase activity, a characteristic of transforming or transformation prone cells, was observed in HCV core- transfected primary human hepatocytes that acquired an immortalized phenotype. In line with this observation, somatic mutation in the

TERT promoter that enhance TERT expression were shown to be among the earliest and most prevalent neoplastic events associated with all major etiologies including HCV. Host genetic variants are also associated with a high risk of HCC^[65]. *PNPLA3* gene (patatin-like phospholipase domain-containing protein-2) shows a significant association with fatty liver disease in HCV patients having a higher risk of HCC^[66-68]. On a similar pattern, polymorphisms in several other cytokines/receptors genes have been found to be associated with HCC. These are cytokines *TNF- α* , *IL-10*, *IL-23R* and vascular endothelial growth factor (*VEGF*) *etc.* genes. Host responds differently to variation in viral genome. For example, HCV genotype 1a and 1b reported to be associated with HCC^[69].

Epigenetic alterations in HCV induced HCC

Various studies have demonstrated a dysregulation of epigenetic regulatory genes in HCC^[70]. Histone-lysine N-Methyltransferase enzyme (EZH2) is one such an example which is aberrantly expressed in HCC^[71] and this also targets expression of tumor suppressor miRNAs^[72]. The changes in gene methylation were also related with virus induced tumors^[73]. Various tumor suppressor genes including *CDKN2A*, *GSTP1*, *RUNX3*, *APC*, *SOCS-1* and *RASSF1A* are highly methylated in HCC caused by HBV and HCV infection^[74]. Epigenetic alterations in HCC may be mediated by changes in miRNAs and long noncoding RNAs. There are several miRNAs which modulate HCV replication in a positive and negative manner^[75].

Neoangiogenesis in HCV induced HCC

Structural and nonstructural HCV proteins have a direct role in inducing neoangiogenesis. HCV core promotes angiogenesis by upregulating hypoxia inducible factor 1- α which regulates VEGF and cyclooxygenase 2. VEGF is an important endothelium specific growth factor in HCC and for this reason, VEGF level in serum is used as a prognostic factor in HCC^[76]. Angiopoietin-2 is also upregulated by HCV infection^[77].

VIRAL FACTORS

HCV replicates and releases its protein component in cytosol. HCV related proteins which have a major role in regulating viral replication and HCV particle assembly, have been demonstrated to influence several cell signal pathways and metabolic mechanisms indicating their role in cell cycle and cell transformation. Both structural and nonstructural proteins interact with different host cellular proteins to promote malignant transformation of hepatocytes. Based on these studies we describe here the role of each individual HCV protein in the process of cell transformation to malignant liver cell.

Core protein

HCV core protein, which regulates HCV RNA translation and its replication, interacts with component proteins of

various cell-signaling pathways. In addition, this protein modulates host immune response, oxidative stress, lipid metabolism and also apoptosis^[78]. In some recent studies on HCV infected patients, core gene has been found to undergo frequent mutations^[79]. The role of core protein in the development of HCC was studied in transgenic mouse model. The information collected from these studies indicate that core gene overexpression results in steatosis in early life with development of adenoma and HCC in later years^[80]. In few other studies, the presence of steatosis in liver induced by core protein could not be related to HCC development^[29,81]. According to recent reports, core protein shows interference with cellular proteins and it is considered as a major risk factor for the progression of HCC^[82]. Of course, the presence of core protein has been associated with its activation of lipogenic pathway in HCC cases^[83]. Core protein often remains associated with lipid droplets in CHC cases and possibly causes steatosis through several mechanisms including peroxisome proliferator-activated receptor alpha and sterol-regulatory element binding protein-1 pathways^[46,81,84].

Similarly, core protein also interacts with ER or mitochondria and induces ER stress by accumulation of ROS^[85]. ROS causes DNA damage and accelerates hepatocarcinogenesis. The effect of HCV core have also been demonstrated on signaling pathways responsible for cell cycle like stimulation of G₁/S transition by increasing the levels of cyclin E/Cdk2^[86] and apoptosis. Core protein interacts with tumor suppressor including P53, P73 and P21^[87] as well as regulator of apoptosis like TNF- α signaling or Bcl-2 members. Core proteins also effects growth and proliferation of cells through activation of signaling pathways like RAF/MAPK (Mitogen activated protein kinase)^[88], Wnt/ β -catenin and TGF- β ^[39,89]. All these pathways have been reported to be active in HCC. Therefore, these findings about HCV core indicate that this protein has a potential role in cell proliferation and reduction of apoptosis during development of HCC.

E1/E2 protein

The effect of structural proteins E1/E2 was also studied on malignant transformation of hepatocytes. The results indicated these proteins to interfere with Interferon actions by inhibiting dsRNA protein kinase (PKR)^[90,91]. In addition, E2 protein also inhibits activation of T and NK cells^[91] and MAPK/extracellular signal regulated protein kinase pathway including the transcription factor ATF-2 and promotes cell proliferation and cell survival^[92].

NS2 protein

NS2 activates cyclin D/CDK4 and induces expression of Cyclin E^[93]. Some studies also supported its role in the inhibition of apoptosis by interference with p53 pathway.

NS3 protein

The NS3 transforms mammalian cells but its role in

HCC is less clear^[94,95]. This protein interacts with tumor suppressor p53. NS3 protein modulates various signal transduction pathways having transformation potential. NS3 interacts with protein kinase A and inhibits its translocation to nucleus. NS3 also inhibits interferon response factor (IRF-3) mediated induction of type-1 interferon, necessary to escape immune surveillance. NS3/4A interacts with ATM, Check point kinase, preventing DNA repair. This also disturbs endoplasmic reticulum leading to cell death^[96]. Similarly, NS3/4A target adaptor molecules in TLR3 and RIG-1 signal pathway, thereby interfering with activation of IRF-3 transcription factor and promoting proliferation^[97-99]. All these reactions contribute to cancer promoting effect of HCV.

NS5A protein

This protein is needed for replication of HCV genome. It forms part of viral replicates complex. Inside the nucleus, NS5A acts as transcription factor activator^[100] and interacts with various signaling pathways including cell cycle/apoptosis, lipid metabolism^[46,101] and also shares some signaling targets with core. It has been reported to interfere with PKR-p38 signaling pathway and inducing aberrant mitosis and chromosomal instability leading to HCC^[102]. NS5A inhibits TGF- β signaling by preventing nuclear translocation of SMAD proteins down regulating tumor suppressor CDKN1A^[103]. On a similar pattern, NS5A inhibits tumor necrosis factor- α (TNF- α) mediated apoptosis^[104]. NS5A acts a transcriptional activator for many genes including p53. NS5A also interacts with pathways like Bcl-2, PI3K, Wnt/ β -catenin signal and mTOR for proliferation of cells and inhibition of apoptosis. It has been found that HCV NS5A influences EMT pathway and helps in transition process of epithelial cells to mesenchymal stem cells. NS5A work in cooperation to TGF- β to activate stellate cell causing fibrosis. Also HCV core protein was found to induce EMT in primary hepatocyte by suppressing cytostatic effect *via* SMAD3^[105,106]. Thus NS5A and core produce cells in tumor mass that are not differentiated and mobile *via* EMT pathway EMT contributes to liver fibrosis on the line as in lungs, kidney and intestine.

NS5B protein

NS5B binds with Rb and promotes its cytoplasmic relocation and proteasomal degradation^[107,108]. This finally activates E2F responsive genes, which in turn stimulates cell cycle progression^[108].

Above reports demonstrate a clear effect of HCV-related proteins on various pathways engaged in progression of infected cells to malignant cells. These proteins enhance the level of underlying inflammation, oxidative stress, ER stress, steatosis, fibrogenesis and finally cell proliferation. Although it is not possible to emphasis their direct effect in exclusion either on initiation or progression, but there is no doubt that involvement of these proteins at various steps of complex

mechanism, helps in progression of carcinogenesis resulting in development of HCC.

CONCLUSION

This update on the development of HCC following chronic HCV infection demonstrates that HCV infection is a serious health problem recorded globally. A majority of patients progress to end stage liver diseases including liver cirrhosis and HCC. Once established, the chronic HCV infection produces several changes in the liver including chronic inflammation, insulin resistance, oxidative stress, steatosis and continuing liver fibrosis. These changes are caused by the mechanism influenced either directly or indirectly by HCV particles. HCV related proteins interact with several cellular proteins thereby modulating cell signaling. Similarly, chronic inflammation caused by HCV inflammation also promotes all above liver changes. During this interplay of various reaction cascade there is possibility of genomic imbalance disturbing the normal reactions leading to abnormal cell cycle and apoptosis. The cumulative effect of all these finally facilitates the tumorigenesis in liver causing HCC. Although several lines of information are available, however, much more still needs to be answered to extricate this mystery.

ACKNOWLEDGMENTS

We appreciate the infrastructure provided by All India Institute of Medical Sciences, New Delhi, India, for conduct of this study.

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