Review Article

Pathogenesis of hepatitis C virus-related hepatocellular carcinoma: evidence from recent studies

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Abstract: Hepatocellular carcinoma (HCC) represents primary liver cancer and is problematic worldwide because it is the major reason for cancer-related death. Various risk factors for developing HCC include advanced liver fibrosis, alcohol abuse, non-alcoholic steatohepatitis (NASH), primary biliary cholangitis, and autoimmune hepatitis. Particularly, infection of chronic hepatitis virus is an important risk factor for HCC, although viral activities could be efficiently controlled with the use of oral medications. Hepatitis C virus (HCV) often provides chronic and persistent infection, leading to chronic liver disease and cirrhosis. There are possible mechanisms of HCV-related HCC development, which include, immune response, inflammation, fibrosis, lipid metabolism and steatosis, neoangiogenesis, and genetic and epigenetic factors, being associated with high cancer incidence. These factors influence the development of HCC dependently and/or independently. Although this is an era of direct-acting antiviral (DAA) therapies, which could have the power to eliminate HCV, the number of patients with a history of HCV infection still require cancer surveillance even after HCV clearance. This review article focuses on the pathogenesis of HCV-related HCC, which may provide informative knowledge and facilitate the understanding of HCV-related oncogenesis. Also, it overviews recent basic and clinical studies regarding the issue and discusses the future perspective of the management of these patients.

Keywords: Hepatitis C virus (HCV); chronic hepatitis; cirrhosis; hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is problematic worldwide because it is the major reason for cancer-related death (1,2). Previous studies have shown that the various risk factors for developing HCC include advanced liver fibrosis, alcohol abuse, non-alcoholic steatohepatitis (NASH), primary biliary cholangitis and autoimmune hepatitis. Particularly, infection of chronic hepatitis virus is a major risk factor for HCC, although it is now an era where viral activities can be controlled with oral medications.

Hepatitis C virus (HCV) often provides chronic and persistent infection, leading to chronic liver disease, and resulted in 475,000 deaths in 2015 (3). The global HCV prevalence was estimated to be 1.0% in 2015 and almost 71.1 million people are infected with HCV. In addition, an estimated 1.75 million new HCV infections occurred in 2015 (4). Approximately 10–20% of patients with chronic HCV infection develop complications, such as cirrhosis, liver failure, and HCC over a period of 20–30 years (5).

There are possible mechanisms of HCV-related HCC development (*Figure 1*), which include, immune response, inflammation, fibrosis, lipid metabolism and steatosis, neoangiogenesis, and genetic and epigenetic factors,

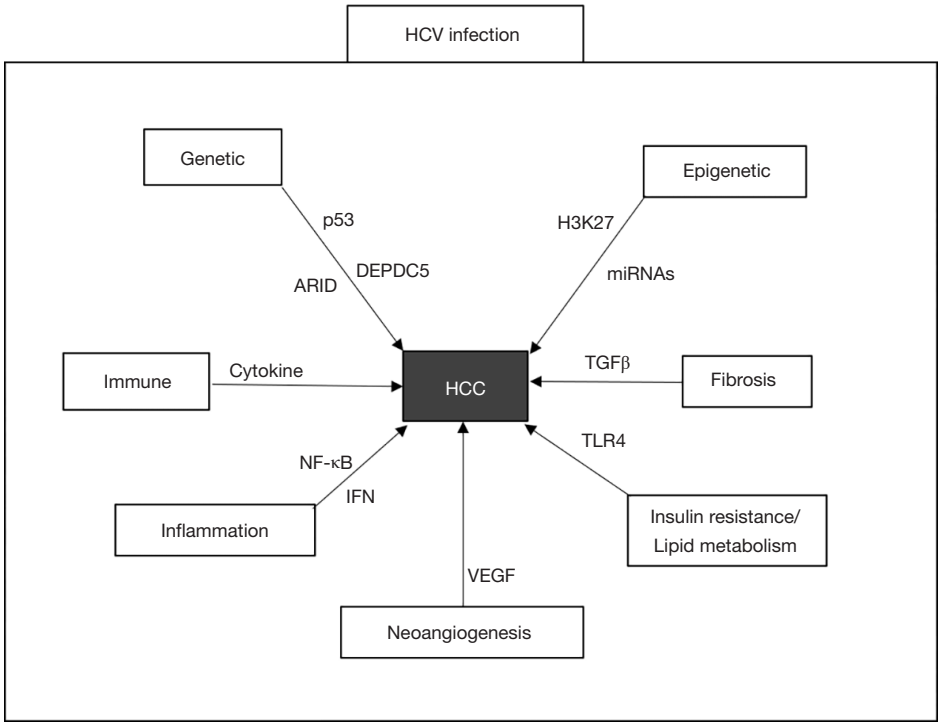

Figure 1 Pathogenesis of hepatitis C virus-related hepatocellular carcinoma.

being associated with high cancer incidence (1% to 7% per year) (6,7). These factors influence the development of HCC dependently and/or independently. This review article focuses on the mechanisms of HCV-induced HCC, which may provide informative knowledge and facilitate the understanding of HCV-related oncogenesis. Also, it overviews recent basic and clinical studies regarding the issue and discusses the future perspective management of these patients.

Immune response

In general, chronic liver inflammation and immune/inflammatory response stimulate the development of HCC (8). Chronic HCV infection with prolonged innate immune activation may influence the success of adaptive immune responses, which differs from those with hepatitis A and B viruses (9). The host regulatory immune response due to a HCV infection may account for hepatic inflammation, and the impaired immune-base surveillance and immunological escape of neoplastic cells enhance development of HCC (10).

For example, patients with HCC showed a higher index tumor necrosis factor (TNF)-α/interleukin (IL)-10 ratio, suggesting that an unbalanced production of cytokines may represent progression to the liver disease severity of HCV-infected patients (11). The IL-6 may also have a role in the development of HCC, as a increased IL-6 seemed an independent risk factor for HCC in female but not male patients with chronic HCV infection (12). In addition, cytokines such as lymphotoxin (LT) alpha and beta and their receptor (LTbetaR) are upregulated in hepatitis B virus (HBV)- or HCV-induced hepatitis and HCC (13).

There is an increase in CD3(+), CD4(+), CD8(+), and CD20(+) liver-infiltrating lymphocytes in HCV-related HCC tissue than in HCV-related cirrhotic tissue, meanwhile the number of CD56(+) cells was significantly reduced. Also, there is an increased gene expressions of CD8α, FoxP3, and RANTES in HCV-related HCC tissue than in HCV-related cirrhotic tissue. Further, a number of CD8(+) cells ≥100/field seems related to an increased tumor recurrence and decreased 5-year overall survival. It has been suggested that elevated densities of liver-infiltrating lymphocytes in liver tissue of HCV-related cirrhosis may contribute to hepatic carcinogenesis and tumor recurrence (14).

Okwor *et al.* reported that patients with fibrosis grade of F3-F4 had higher frequencies of >3 inhibitory receptor co-expression on natural killer (NK) cells in patients with chronic HCV infection (15). Moreover, F3-F4 patients

manifest a higher frequency of NK cells co-expressing T cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain and T cell immunoglobulin and mucin-domain containing-3, and CD4/NK cells co-expressing lymphocyte activation gene 3 and Galectin-9. Taken together, the interactions between inflammation by tumor promotion and the dysregulation of anticancer immunity may account for the HCC development in patients with HCV-related cirrhosis.

Inflammation and fibrosis

Chronic inflammation by HCV infection may provide an indirect effect on hepatocarcinogenesis, as well as an increase of reactive oxygen species (ROS), which leads to hepatocellular damage or death. An antiviral host defense response may also account for the inflammation by the release of interferon (IFN), typically IFN-γ and other cytokines (16). The major regulation of immune response to hepatitis viruses are conducted by NF-κB-related and/or IFN-related signaling, partly through the JAK-STAT pathway (17-19). Obviously, *in vivo* inflammation is a protective response and viral replication is responsible for repairing tissues damaged by the virus. However, the intrahepatic repair response may provide the replication of inactive hepatocytes, some of which may show oncogenic mutations that have the possibility of leading to the hepatocarcinogenesis (20).

Chronic inflammation due to HCV infection accounts for the development of liver fibrosis, which is a risk factor for the occurrence of HCC. One of the mechanisms for hepatic fibrogenesis may be dependent on a HCV core protein via the up-regulation of connective tissue growth factor (CTGF) and transforming growth factor (TGF)-beta1, which result in an increased risk for HCC via pSmad3L by affecting hepatocytic TGF-beta signaling (21,22). In fact, a higher level of plasma TGF-beta 1 was demonstrated in patients with HCC than in those patients with chronic hepatitis and cirrhosis, suggesting the role of plasma TGF-beta 1 as a novel tumor marker for HCC (23). However, detailed mechanisms to explain the relationship between the progression of liver fibrosis and cancer development needs to be clarified.

Lipid metabolism and steatohepatitis

The HCV infection is closely related to the development of liver steatosis/steatohepatitis (24,25). Furthermore, the accompanied altered lipid metabolism may be related to the development of HCC (26,27). A study using human liver samples showed marked elevation of mRNA expression for lipogenic enzymes, such as fatty acid synthase, acetyl-CoA carboxylase, and adenosine triphosphate (ATP) citrate lyase in HCC as compared with surrounding non-cancerous liver tissue (28). Extreme obesity and diabetes are also related to a risk of HCC in patients with HCV infection (29). Actually, a recent study demonstrated interesting data to support the relationship between steatosis and HCC development; a dose-dependent decrease in incident cirrhosis and HCC by using statin in patients with chronic HCV infection (30).

Investigators have shown the basic mechanisms of HCC development due to HCV infection accompanied with obesity/alcohol abuse. Mice with defective TGF-β signaling [Spnb2(+/-) mice] exhibited enhanced liver Toll-like receptor 4 (TLR4) expression and developed HCC in a TLR4-dependent manner (31). NANOG is induced by TLR4 signaling through the phosphorylation of E2F1, and its downregulation slowed down HCC progression induced by an alcohol western diet and HCV protein in mice (32). Moreover, HCV-NS5A combined with a Western diet which is rich in cholesterol and saturated fat enhanced the TLR4-NANOG and leptin receptor (OB-R)-pSTAT3 signaling pathways resulting in liver carcinogenesis via mesenchymal phenotype with prominent Twist1-expressing TICs (33).

In nonalcoholic fatty liver disease (NAFLD), hepatocellular LTβR and canonical NF-κB signaling enhances an occurrence of HCC from nonalcoholic steatohepatitis (NASH) (34). A dysregulation of lipid metabolism in NAFLD caused a selective loss of intrahepatic CD4(+) but not CD8(+) T lymphocytes, leading to accelerated hepatocarcinogenesis (35). Altogether, these data suggest that potential various mechanisms through multiple pathways account for the development of HCC caused by impaired lipid metabolism due to HCV infection.

Neoangiogenesis

Hypervascularity is a typical hemodynamic appearance of HCC, supported by studies showing increased microvascular density in patients with HCV-related liver diseases (36,37). Hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) are known as significant regulators of angiogenesis. A clinical study using the SHARP-study cohort demonstrated that the angiogenesis biomarkers Ang2 and VEGF were independent predictors

of survival in patients with advanced HCC (38). A basic study performed later supported these data by reporting on the role for the HCV core protein on activating HIF-1α, leading to the stimulation of VEGF, whose overexpression was demonstrated in HCC tissue (39). According to the study by Yvamoto *et al.*, VEGF-C936T polymorphism was not related to HCC, but the mutant allele (T) was linked with the increased VEGF levels in patients with HCC. Logically, VEGF may play a role as a biomarker for HCC, however alfa fetoprotein (AFP) may be applicable to differentiate between patients with HCC and those with HCV infection or cirrhosis (40).

Genetic

Investigators have shown the influence of gene mutations on hepatocarcinogenesis (41). An expression or abnormal form of the protein of p53, known as a tumor suppressor gene, are frequently associated with HCC cell lines (42). Recent well-designed studies have shown the association of mutations in some specific genes: Telomerase reverse transcriptase (TERT) gene affecting the promoter region (43,44); ARID2 inactivation mutations in 18.2% of individuals with HCV-associated HCC in the United States and Europe (45); and ARID1A, ARID1B, ARID2, MLL, and MLL3 (46). In addition, mutations in RPS6KA3-AXIN1 and NFE2L2-CTNNB1 suggest that Wnt/β-catenin signaling may cooperate in hepatocarcinogenesis with both oxidative stress metabolism and Ras/mitogen-activated protein kinase (MAPK) pathways (47).

More recent studies detected IFN-related gene polymorphism, and impaired genotypes for the clearance of HCV close to IFNL3 were related to the risk of HCC development, showing the adjusted odds ratio of 1.73 (1.00–2.99) for rs12979860 and 1.84 (1.02–3.33) for rs8099917 (48,49). Polymorphisms in cytokines also account for the risk of HCC development: Decreased haplotypes of IL-10 and TNF-α GG genotype (50), wild type IL-23R GG (51), and GG, GG+GA genotypes of IL17A gene (52). Additionally, a variation in the DEPDC5 locus was related to the progression to HCC in chronic HCV carriers (53), and the risk allele of rs2596542 was associated with lower soluble MICA protein levels in individuals with HCV-induced HCC (54).

HCV isolated with core-Gln(70) and/or NS3-Tyr(1082)/Gln(1112), which are more closely related to HCC development (55), and the genetic variety of HCV were dominant in livers with HCCs compared with those of control or negative HCC (56).

Ibrahim *et al.* reported the relationship between SNPs in three genes related to the early immune response against HCV and the risk of progressive liver disease: Low molecular mass polypeptide 7 (LMP-7), IL28B, and 2'-5'oligoadenylate synthetase 1 (OAS1). Particularly, SNPs in LMP-7 and IL28B rs12979860 were linked with the development of HCC (57).

A more recent study has shown that elongation factor Tu guanosine triphosphate binding domain containing 2 which is a new host factor with activity against HCV infection has a role as a novel oncogene that helps to maintain the survival of HCC cells and promotes HCC progression through the activation of signal transducer and activator of transcription 3 (58). Further, a study in Egypt demonstrated that both allelic and genotypic variations of the chitinase-3-like protein1 gene (rs880633) and an intergenic (rs597533) seemed to be significant predictors confirming a great risk for HCC susceptibility in patients achieved sustained virological response (59). These findings strongly suggest the importance of host genetic factors in the development HCC due to of HCV infection.

Epigenetic

There is a close linkage between the altered regulation of epigenetic mechanisms and the development of HCC (60-63). The histone H3 lysine 27 (H3K27) tri-methylating enzyme, enhancer of zeste homolog 2 (EZH2) mRNA expression was upregulated in human HCCs and may play an important role in tumor progression, especially by facilitating portal vein invasion (64). In addition, EZH2 exerts its prometastatic function by way of epigenetic silencing of multiple tumor suppressor miRNAs (65). HCV-induced overexpression of protein phosphatase 2A (PP2Ac) also contributes to hepatocarcinogenesis through the dysregulation of epigenetic histone modifications [inhibition of histone H4 arginine methyltransferase 1 (PRMT1)] (66).

Investigators have shown strong evidence for hepatocarcinogenesis in viral-related liver diseases by silenced tumor suppressor genes through epigenetic disruption (such as promoter CpG island methylation, RUNX3, SOCS-1, GSTP, APC, E-cadherin, and p15) (67-69). Different epigenetic changes in different viral etiologies have also been reported. HOXA9, RASSF1, and SFRP1 dominant in HBV-positive HCC cases, while CDKN2A is often methylated in HCV-positive HCC cases (70). A more recent study reported that HCV infection or core protein induces homeobox genes by impairing histone H2A monoubiquitination via a reduction in the ring finger

protein 2 level, reading to hepatocarcinogenesis (71).

MiRNAs are small noncoding RNAs with an average of 22 nucleotides that mainly regulate gene expression. Altered expression of miRNAs in the liver may be related to the occurrence/development of various liver diseases. Up-regulation of miR-155 may have a role in hepatocyte proliferation and carcinogenesis in chronic HCV-infected patients and HCV-related HCC (72), and a relationship between the up-regulation of miR-224 and cell migration/invasion in HCC has also been reported (73). A more recent study reported that miR-26a, miR-122, and miR-130a were down-regulated in the HCC tissue, and the up-regulated gene targets were primarily related to aberrant cell proliferation that involved DNA replication, transcription, and nucleotide metabolism (74). Meanwhile, miR-21, miR-93, and miR-221 were up-regulated in HCC, and the down-regulated gene targets were primarily linked to metabolism and immune system processes (74). These works indicate that miRNAs may be potential effective biomarkers for the evaluation of HCC, however, candidate miRNAs vary. Further investigation is warranted in the future.

Conclusion

HCV-induced HCC is a well-defined target for cancer prevention. However, the mechanism of HCC development due to HCV infection is complicated with multiple possible pathways, accompanied by the interactions between host and viral responses. Moreover, the detailed processes between the progression of liver fibrosis and cancer development is still controversial and needs more investigation. Although this is an era of direct-acting antiviral (DAA) therapies, which could have the power to eliminate HCV, the number of patients with a history of HCV infection still require cancer surveillance even after HCV clearance (75). Continuous research is necessary to improve the quality of medical care, by using effective monitoring and surveillance of high-risk patients with genetic/epigenetic factors and metabolic aspects, and the application of anticancer immunotherapy.

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Footnote

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