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REVIEW

Molecular pathways in viral hepatitis-associated liver carcinogenesis: An update

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of cancer among primary malignant tumors of the liver and is a consequential cause of cancer-related deaths worldwide. In recent years, uncovering the molecular mechanisms involved in the development and behavior of this tumor has led to the identification of multiple potential treatment targets. Despite the vast amount of data on this topic, HCC remains a challenging tumor to treat due to its aggressive behavior and complex molecular profile. Therefore, the number of studies aiming to elucidate the mechanisms involved in both carcinogenesis and tumor progression in HCC continues to increase. In this context, the close association of HCC with viral hepatitis has led to numerous studies focusing on the direct or indirect involvement of viruses in the mechanisms contributing to tumor development and behavior. In line with these efforts, this review was undertaken to highlight the current understanding of the molecular mechanisms by which hepatitis B virus (HBV) and hepatitis C virus (HCV) participate in oncogenesis and tumor progression in HCC and summarize new findings. Cumulative evidence indicates that HBV DNA integration promotes genomic instability, resulting in the overexpression of genes related to cancer development, metastasis, and angiogenesis or inactivation of tumor suppressor genes. In addition, genetic variations in HBV itself, especially preS2 deletions, may play a role in malignant transformation. Epigenetic dysregulation caused by both viruses might also contribute to tumor formation and metastasis by modifying the methylation of DNA and histones or altering the expression of microRNAs. Similarly, viral proteins of both HBV and HCV can affect pathways that are important anticancer targets. The effects of these two viruses on the Hippo-Yap-Taz pathway in HCC development and behavior need to be investigated. Additional, comprehensive studies are also needed to determine these viruses' interaction with integrins, farnesoid X, and the apelin system in malignant transformation and tumor progression. Although the relationship of persistent inflammation caused by HBV and HCV hepatitis with carcinogenesis is well defined, further studies are warranted to decipher the relationship among inflam-

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masomes and viruses in carcinogenesis and elucidate the role of virus-microbiota interactions in HCC development and progression.

Key Words: Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinoma; Carcinogenesis; Molecular pathways; Viral hepatitis.

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Core Tip: Hepatocellular carcinoma remains an aggressive tumor, despite extensive studies on its ontogeny and prognosis. Although the occurrence of this tumor in both hepatitis B virus (HBV) and hepatitis C virus (HCV) backgrounds indicates the effect of persistent inflammation in malignant transformation, the viral effects are not limited to the impaired microenvironment. Recent studies have revealed complex mechanisms that reflect concerted and cumulative effects of chronic inflammation-related alterations, modification of oncogenic pathways (especially tumor suppression, proliferation, and apoptosis), and epigenetic dysregulation driven by both HBV and HCV. In addition, the integration of HBV into host DNA may also affect tumor development and behavior.

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INTRODUCTION

Primary liver cancer is a major global health problem. Its incidence and mortality are increasing, in contrast to the decreasing incidence of many organ cancers worldwide. Indeed, hepatocellular carcinoma (HCC), which accounts for 90% of liver malignancies, is the 5th and 9th most common cancer in men and women, respectively, and is the 3rd leading cause of cancer-related deaths[1,2]. Despite extensive research on its diagnosis and treatment, difficulties in early diagnosis and a lack of specific medical treatment in advanced stages have led to HCC continuance as an aggressive tumor with a poor prognosis.

Although risk factors associated with the development of HCC are numerous, the damage caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections plays a large role in the development and progression of HCC[1]. In this context, the detection of HBV and HCV in 50% and 30% of patients with HCC, respectively, and the higher prevalence of HCC in endemic regions of the world are strong indicators supporting the relationship between HCC and viral infection[3-6]. In addition, among patients with HBV infection worldwide, higher rates of HCC development and mortality in patients with a coinfection of HBV (24%) or HCV (1%) compared to those with HVB monoinfection also support the contribution of viruses to oncogenesis and tumor behavior[7-10]. Therefore, defining the mechanisms by which viruses participate in molecular events in HCC development and progression is paramount for identifying new treatment targets.

This review aims to provide an overview of basic and clinical studies dealing with the molecular regulation and cell biology of HBV and HCV that affect carcinogenesis and tumor behavior in HCC. Additionally, it addresses the current understanding of existing mechanisms to facilitate the identification of new therapeutic targets and strategies to combat this disease.

GENERAL FEATURES OF THE VIRUSES

HBV

This virus is a member of the hepadnaviridae family with cellular tropism for hepatocytes[11-13]. HBV has a compact, partially double-stranded relaxed circular

DNA genome (rcDNA) containing four overlapping open reading frames[14]. Viral protein products include three surface proteins [also known as large/pre-S1 (L-HBsAg), medium/pre-S2 (M-HBsAg) and small/major (S-HBsAg)], a core antigen (HBcAg), secreted "e" antigen (HBeAg), viral polymerase (reverse transcriptase, DNA polymerase, and RNaseH activity) and protein X (HBx), which play an important role in HBV pathogenesis and viral transcription[14].

Determination of viral genotypes in HBV has also been found to play an important role in assessing HCC risk. Among the ten subgenotypes of HBV (A to J), HCC risk from highest to lowest is ranked as genotypes C, B, F, D, and A[6,15]. It has been suggested that core promoter mutations (T1762/A1764) convey a higher risk for developing HCC, particularly in young and noncirrhotic subjects infected with HBV genotype B or C[16]. Finally, there is also evidence that in genotype C infections, the development of HCC can be predicted by mutations/deletions in the preS region[17]. Comprehensive information regarding viral replication and other features of HBV is available in many recent studies.

HCV

HCV, part of the Flaviviridae family, is a single-stranded RNA virus[18]. HCV infects hepatocytes because they contain both essential entry receptors and suitable cellular host factors (miR-122) for the virus[19,20]. As a function of HBV, three structural proteins (core, E1, and E2), as well as seven nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B), are involved[18]. Recently, two mini-core proteins containing the C-terminal portion of the p21 core nucleocapsid (but lacking the N-terminus) and translated from an alternative open reading frame at amino acids 70 and 91 have been described[21,22]. Their mutations were found to be correlated with an increased risk of HCC, insulin resistance, and failure of interferon therapies. Following viral replication and protein translation, the core protein is collected on a lipid droplet in the ER, allowing the nucleocapsid to form by collecting the encapsulated HCV to release the viral particles associated with very low-density lipoproteins from the cytoplasm[23-25]. These data are all evidence for the dependence of HCV on lipoproteins for survival.

There are 6 main genotypes (1 to 6) of HCV. However, findings regarding the HCV genotype and the risk of HCC development differ[6,10]. In the United States, HCV genotype 3 infections have been observed as conveying a higher risk for developing HCC than genotype 1 infections. Another study from Asia reported an increased risk of genotype 6 infections[26,27]. Although geographical distribution appears to affect these data, further studies are needed to examine the relationship between HCV genotypes and HCC risk.

HBV-RELATED CARCINOGENESIS

HBV DNA integration in host chromosomes

The integration of HBV DNA into host chromosomes is not an essential step in the HBV life cycle. However, this phenomenon promotes the stimulation of carcinogenesis by causing instability of the host chromosomes and increasing the expression of genes related to cancer development, metastasis, and angiogenesis, or by inactivating tumor suppressor genes. Since the 1980s, when the integration of HBV DNA into the host genome was first reported, the genomic integration regions on the chromosomes have long been thought to be random. In recent years, whole-genome sequencing techniques of tumor tissues have revealed repetitive integration spots. In tumor tissues from patients with HBV-HCV, HBV DNA integration was observed in 80% of cases, and the frequency of integration was significantly higher in HCC than in nontumor areas[28,29]. Moreover, the integration sites in tumors tend to be in the vicinity of important promotor regions, such as CpG islands and telomeres, suggesting that preferential targeting of these regions is related to gene regulation[29-31]. Target genes affected by HBV genome integration include the following: tumor suppressor protein 53; telomerase reverse transcriptase; catenin beta 1 (CTNNB1); retinoic acid receptor beta; catenin delta 2; Axin1; AT-rich interactive domain-containing protein 1A (ARID1A); ARID1B; ARID2; myeloid/Lymphoid or mixed-lineage leukemia 3 (MLL3); MLL4; cyclin E1; cyclin A2; protein tyrosine phosphatase receptor type D; and unc-5 netrin receptor D[32-36]. Neuregulin 3, aryl-hydrocarbon receptor repressor, SUMO-specific peptidase 5, rho-associated coiled-coil containing protein kinase 1, fibronectin, angiopoietin 1 calcium signaling-related genes, platelet-derived growth factor, apoptosis-related genes, and ribosomal protein 60S-like genes are also affected by HBV

[37-41].

On the other hand, the integration of HBV DNA into host chromosomes often results in fragmentation, rearrangement, and degradation of the viral genome, leading to structural alterations. The most frequent change occurs with a high frequency of integration in the HBx coding sequence, leading to the formation of chimeric transcripts containing both viral and host sequences and the expression of C-terminally truncated HBx[30,42,43]. This form of HBx has been shown to contribute to expanding cell lines with cancer stem cell-like properties, induce Wnt-5a, and participate in metastasis and cell proliferation[44-47]. It also stimulates oxidative DNA damage and promotes MMP-10 expression[48-50]. Additionally, it can also counteract the growth-suppressive and apoptotic effects of full-length HBx[51,52]. Hybrid transcripts formed by integration with host DNA (HBx-LINE1, HBx-S protein-coding region breaks, and truncated preS/S proteins) may also have an oncogenic effect[34,42,53].

HBV induced epigenetic dysregulation

Epigenetic changes include all chromatin changes, which can be reversible according to physiological conditions that include three interactive types, DNA methylation, histone modification, and RNA-related silencing without any changes in the DNA sequence.

DNA methylation: In addition to epigenetic modifications of HBV DNA itself, HBV may also play a role in the methylation of genes that affect the activation of pathways involved in carcinogenesis development. In HBx-transgenic mice, the contribution of hypomethylation of GpG islands to the downregulation of E and N-cadherins involved in epithelial-mesenchymal transition (EMT) was demonstrated[54]. This hypomethylation also affects Smad6 and Kcp, which are involved in Smad-dependent TGF-β and Wnt signaling pathways[54]. Moreover, genes with important roles in HCC development such as p16 (INK4A), GSTP1, CDH1 (E-cadherin), RASSF1A, and p21 (WAF1/CIP1), can be affected by HBV methylation[55]. In cell cultures, decreased transcriptional activity of CD82, which is both a tumor and metastasis suppressor, by HBV-mediated methylation also emphasizes the importance of viral-induced hypomethylation in carcinogenesis[56]. Ankyrin repeat-containing, SH3 domain-containing, and proline-rich-region-containing protein (ASPP) family members are newly identified apoptosis regulatory proteins. Recently, downregulation of the *ASPP1* and *ASPP2* genes was correlated with HBV-related DNA methylation in HCC-HBV[31]. In addition, HBx, which increases the recruitment of DNA methyltransferase 1 (DNMT1) and DNMT3a to ASPP2, influences the host genome in carcinogenesis. Furthermore, after the suggestion that HBx plays a role by increasing the recruitment of DNMT1 and DNMT3a to the promoter region of ASPP2 during methylation, many studies have shown that the effect of HBx on host promoter methylation is associated with oncogenesis and tumor behavior[31]. The HBx protein contributes to tumor aggressiveness by methylating the CpG1 island that contains the P53 repressor and metastasis-associated protein 1 (MTA1) promoters by recruiting DNMT3a and DNMT3b. Similarly, it participates in oncogenesis by methylating the SOCS-1 tumor suppressor[57,58]. HBx can modulate oncogenesis and tumor behavior by modulating tumor suppressors, such as RASSF1A, protocadherin-10, insulin-like growth factor-binding protein 3, and E-cadherin[59-62].

Histone modifications: For gene regulation, acetylation is important for the posttranslational modifications of histones and involves the transfer of acetyl groups from acetyl-CoA to lysine residues on their N-terminal tail. This phenomenon is regulated by histone acetyltransferases and histone deacetylases (HDACs) and allows the binding of trans-acting factors to promote gene activation. In particular, increased expression of HDACs can contribute to oncogenesis due to their negative effects on suppressor genes[63,64]. In an elegant study, Liu *et al*[65] demonstrated that HBx binds to methyl-CpG binding domain protein 2 (MBD2) and the transcriptional coactivator CREB1 binding protein (CBP)/p300, leading to activation of insulin-like growth factor 2 (IGF-2) in HCC. They also demonstrated that HBx promotes hypomethylation and acetylation of histone H4 in the IGF-2 promoter and facilitates the formation of the MBD2-HBx-CBP/p300 complex, leading to transcriptional activation.

MicroRNAs in HBV: MicroRNAs (miRs) are small noncoding RNA molecules involved in gene silencing, and their modulation in the liver is associated with hepatocarcinogenesis and tumor behavior, similar to many other cancers. In HBV-HCC, it has been noted that while the expression of miR-224, miR-545, miR-374a, and the miR-17-

92 polycistron is increased[66-68], the expression levels of miR-145, miR-199b, let-7a, and miR-152 are decreased[67,69-71], supporting the distinct roles of miRs in these processes. Recently, upregulation of miR21, which is highly expressed in HBV-HCC, was found to be induced by HBx, leading to increased cell proliferation by inhibiting programmed cell death protein-4 and PTEN[72,73]. Li *et al*[74] suggested that miR21 upregulation is dependent on stimulation of IL-6, facilitating STAT3 activation. In the liver, impaired lipid metabolism results in cellular damage and lipid accumulation involved in oncogenesis. In HCC, the levels of miR205, which regulates the expression of acyl-CoA synthetase long-chain family member 1 (an important lipid metabolism enzyme), decrease, leading to excessive lipid synthesis and accumulation[75,76], and the suppressive effect of HBx on miR205 has also been demonstrated. The results of a recent comprehensive study on the alterations of miRs in the liver suggest that different miRs are involved during the different steps of hepatocarcinogenesis[77]. In HBV-HCC, the expression of miR-150, miR-342-3p, miR-663, miR-20b, miR-92a-3p, miR-376c-3p, and miR-92b was found to be altered. However, in HBV, alterations in miR-98, miR-375, miR-335, miR-199a-5p, and miR-22 have been described. There is evidence that some of these miRs may be potential biomarkers for detecting HCC developing in HBV backgrounds, while others may represent therapeutic targets[69]. However, further studies are warranted to elucidate the biological significance of alterations in miRs during oncogenesis.

Genetic variations in HBV

HBV DNA polymerase is predisposed to errors, which can result in mutations in all four genes in the viral genome[30]. As described above, HBsAg proteins are in the form of three envelope proteins, L-HBsAg, M-HBsAg, and S-HBsAg. While L-HBsAg is involved in viral binding to the hepatocyte surface, the function of M-HBsAg is not fully understood. Nevertheless, increasingly more findings indicate that M-HBsAg deficiency does not affect viral replication or maturation. Among these three proteins, the most frequently observed S-HBsAg protein has its primary hydrophilic region (MHR) located between amino acids 99 and 169, containing the major antigenic determinant (determinant "a") between amino acids 127-147[30,31,77]. It has been shown that mutations in this determinant can lead to escape from vaccine-induced immunity[78]. In addition, various MHR mutations may lead to the reactivation of viral infection after an immunosuppressive therapy or may reduce the antibody development and antigenicity of HBsAg[79,80]. On the other hand, mutations in the preS sequence have been detected in the serum and tumor tissues of HBV-HCC patients[81,82]. PreS deletions may also disrupt the interaction of L-HBsAg with S-HBsAg[83]. This may lead to retention of the L-HBsAg protein in the ER. Indeed, ground glass hepatocyte formation in HBV hepatitis is caused by the accumulation of the L-HBsAg protein in the ER due to PreS mutation[84-86]. However, the accumulation of L-HBsAg proteins is not limited to ground glass formation but also leads to the induction of ER stress and subsequent oxidative DNA damage followed by malignant transformation with genomic instability[81,82]. Demonstrations of the association among preS or preS2 mutations with increased L-HBsAg expression and borderline dysplastic lesions and HCC development in experimental studies support the involvement of PreS deletions in carcinogenesis[81,87]. Another new mutant formed by the change in the 4th amino acid of the PreS1 protein (from tryptophan to proline or arginine) was found to be associated with an increased risk of HCC[88]. In addition, PreS mutants have also been shown to induce anchorage-independent cellular growth, inflammatory cytokines, the DNA repair gene OGG-1, and the expression of ER chaperones[84,89].

Among the naturally occurring nucleotide mutations involving all four HBV genes, the double nucleotide mutations A1762T and G1764A, which reside in the basal core promoter (BCP), greatly reduce the levels of precore protein mRNA and consequently HBeAg expression[79,90]. This mutant is often found in HBeAg-negative patients with chronic hepatitis[90]. This double mutation transforms a nuclear receptor binding site in BCP into an HNF1 transcription factor binding site and increases HBV replication [91,92]. Mutation of BCP usually occurs in the form of G1896A, which abolishes HBeAg expression by converting codon 28 of the precore sequence into the TAG termination codon[91,93]. This mutation differs across HBV genotypes due to the localization of G1896 in an epsilon (e) structure (stem-loop structure) required for the initiation of pgRNA encapsulation[94]. G1896A mutation is uncommon in HBV genotype A and may lead to destabilization of the (e) structure. However, in other types of HBV, it can increase viral replication by stabilizing the (e) structure[95]. Previous studies have shown that these mutations are associated with high HCC risk,

while other BCP mutations (such as T1753C and C1766T) are associated with carcinogenesis[96-98]. In addition, Yan *et al*[99] showed that these mutations were associated with upregulation of S phase kinase-associated protein 2 and induction of p53 degradation.

The role of HBx protein in HCC

HBx and gene expression: HBx does not bind DNA directly but can interact with multiple transcription factors to alter the expression of host and viral genes. This protein, which plays a crucial role in the prevalence of HCC, is a 154 amino acid peptide chain containing a C-terminal transactivation domain consisting of an N-terminal negative regulatory domain with a molecular mass of 17 kDa. HBx, which is formed from *HBx* gene transcription initiated by integrating viral DNA into the host genome, can be found in different subcellular regions[44]. Therefore, HBx acts differently depending on its subcellular localization within hepatocytes[100]. HBx in the nucleus performs viral replication both by increasing HBV gene expression and preventing HBV gene methylation[101-103]. Within the cytoplasm, HBx affects signaling pathways and transcription factors. On the other hand, it regulates protein degradation, cellular transcription, apoptosis, and cell proliferation by colocalization in the mitochondrial cytoplasm and nucleus[104]. Therefore, it is not surprising that HBx interacts with many factors and pathways directly and indirectly involved in carcinogenesis and tumor progression.

One of HBx's mechanisms of action is its ability to bind to transcription factors involved in oncogenesis and the progression of HCC. These factors include nuclear factor kappa-B (NF-κB), RNA polymerase binding protein, transcription factor II B, transcription factor II H, CBP/p300, activating transcription factor 2, and activating protein-2[105]. Furthermore, the effect of HBx on several transcription factors is not limited to being a binding partner and may further affect their function through distinct mechanisms. For instance, HBx not only binds to the cAMP response element binding protein (CREB) but also facilitates the participation of CREB in viral DNA by interfering with protein phosphatase 1 activity[105,106]. Similarly, HBx interferes with SIRT1, allowing the release of β-Catenin, which enables activation of the expression of cancer-promoting genes, such as cyclin-D1 and c-myc[107].

HBx also regulates gene expression through epigenetic modifications. Restriction of the expression of the secreted frizzled-associated proteins SFRP1 and SFRP5, members of the extracellular glycoprotein family, occurs through epigenetic silencing mediated by HBx[44,108,109]. In this process, HBx facilitates the binding of DNMT1 and DNMT3 to the promoters of these genes, leading to their hypermethylation[109]. Suppression of SFRP1 and SFRP5 allows transactivation of Wnt target genes, including c-myc and cyclin D1, consequently promoting EMT and malignant transformation [109]. The decrease in the expression of both SFRP1 and SFRP5 in HBV-HCC is also in line with these findings[108-110]. SUZ12 and ZNF198 are two transcription repressive complexes held together by binding to the long noncoding RNA HOTAIR. SUZ12 constitutes a subunit of polycomb repressor complex 2 (PRC2), and ZNF198 stabilizes the transcription suppressor complex (LSD1, Co-REST, and HDAC1). The effect of HBx on these two transcription suppressors leads to reduced PRC2 and LSD1/Co-REST/HDAC1 complexes of target genes, such as epithelial cell adhesion molecule (EpCAM), which play an important role in tumor development and progression[111, 112].

HBx and DNA repair: Cells inhibit cell cycle progression by inactivating cyclin-dependent kinases (CDKs) in response to DNA damage. The absence of such a response can cause genetic instability, mutagenesis, and tumor growth. Accumulating evidence indicates that HBx facilitates the accumulation of DNA damage by interfering with cell cycle checkpoints and DNA repair[31]. HBx also affects DNA repair by competing with XPB/D to bind and sequester p53[113]. An important protein in the base excision repair pathway is human thymine DNA glycosylase (TDG), structurally similar to HBx. Van de Klundert *et al*[114] suggested that HBx causes the accumulation of DNA damage and cellular transformation by altering or preventing the function of TDG in the DNA repair process. There is also evidence that HBx stimulates CDK2 and CDC2, which play a role in the transition of the cell to S and M phases, forcing the cell to enter the proliferation cycle.

HBV and cellular signaling pathways in hepatocarcinogenesis

Wnt/β-Catenin pathway: It has been shown that *CTNNB1*, the gene encoding beta-catenin, is mutated in 40% of HBV-HCC cases[115]. Similarly, activation of Wnt/β-Catenin was noted with loss of function due to hypermethylation in the tumor

suppressor APC gene, which is an important component of this pathway[116,117]. Detection of different expression levels of components in the canonical Wnt/β-Catenin pathway in HBV-related HCC (HBV-HCC) has presented findings supporting the role of HBV in oncogenesis. In such cases, higher expression of the regulators of Wnt/β-Catenin (Frizzled 2, Frizzled 7, Segment polarity protein disheveled homolog DVL-3, secreted frizzled-associated protein 4, Wnt-1 inducible signaling pathway protein 1 and fos-associated antigen 1) in tumor tissues compared to nontumoral mucosa and decreases in transducin-like enhancer protein, naked cuticle 1 (*NKD1*) and *NKD2* gene expression indicate notable evidence for the involvement of this pathway in HBV-associated carcinogenesis[109,115-119].

In this context, the HBx protein activates the Wnt pathway by inhibiting E-cadherin in different ways (promoter hypermethylation, changes in SNAIL gene expression, and Src signal activation) and represses SFRP1 and SFRP5[109,115-118]. On the other hand, HBx can disrupt the degradation of β-Catenin through its ability to bind with APC. Again, inhibiting the GSK3b degradation complex and stimulating URG7 causes abnormal activation of the Wnt signaling pathway. As a result, the expression of c-myc, CTFG, and WISP2 increases[120,121]. HBx may also indirectly cause an increase in EpCAM from target genes of this pathway on miRs. It has been suggested that it may contribute to hepatocarcinogenesis, especially with the increase in c-myc oncoprotein[115].

HBsAg affects the Wnt pathway by increasing the expression of lymphoid enhancing factor, a transcription factor in this pathway. Differences in the expression of this factor in nontumor areas and tumors (cytoplasmic *vs* nuclear) indicate the role of HBsAg in the Wnt pathway in carcinogenesis[122]. Viral influences on this pathway are summarized in Figure 1.

NF-κB pathway: NF-κB consists of 5 proteins [NF-κB1 (p105/p50), NF-κB2 (p100/p52), Rel A (p65), cRel and RelB], all of which contain a nuclear localization signal Rel homology region, while some (p65, cRel and RelB) have a transactivation region. More comprehensive information on this factor was presented in a recent review by Shokri *et al*[123], with viral contributions to the NF-κB pathway summarized in Figure 2. The participation of these pathways in very important cellular events, such as growth, differentiation, proliferation, apoptosis, angiogenesis, and immune responses, is supported by demonstrating that aberrant expression of these pathways plays an important role in carcinogenesis and tumor progression. The use of NF-κB inhibitors as a therapeutic target in various cancers suggests that it may also be a suitable treatment option for HCC. However, the effects of viruses on this pathway should be better understood to use these pathways effectively in treatment. HBV activates this pathway through oxidative stress and TNF-α activation. HBx, HBsAg, and HBcAg can cause NF-κB activation by inducing ROS production[124]. By increasing the expression of cytokines, such as IL-6, IL-8, and CXCL2, the HBx protein contributes to inflammation and fibrosis and the development of HCC[125]. It has been demonstrated that activation of NF-κB by HBx is possible by affecting Rel-related and Rel-unrelated proteins. HBx induces a prolonged NF-κB response by decreasing cytoplasmic levels of p105 and p50 and increasing IKBα phosphorylation and degradation and Rel-A release[123,126]. In addition, by replacing p50, HBx can activate the NF-κB pathway[123]. It has been experimentally demonstrated that Rel-A, a component of nucleosome remodeling and the deacetylase complex, can bind to the promoter region of MTA1, leading to increased MTA1 expression and NF-κB activation. Bui-Nguyen *et al*[127] revealed that this situation was associated with invasion and metastasis in HCC. There is also evidence that the TANK-binding kinase responsible for RelA phosphorylation (TBK-1) may also play a role in HBx-associated NF-κB activation[123]. The existing role of the HBx protein in activation of the Wnt-β catenin pathway (see the previous section) may indirectly lead to NF-κB activation. Similarly, HBx may play an indirect role by activating cytoplasmic signaling pathways (PIK3C, Ras/Raf/MAP kinase, Src, and JAK-STAT) that promote the phosphorylation and degradation of IKBα[128]. HBx can also induce NF-κB activation either synergistically by binding to von Hippel-Lindau binding protein or by stabilizing the amplified in breast cancer 1 oncogene, enabling NF-κB signal transition[129]. The effect of HBx has also been shown to be dependent on chaperone proteins, such as ribosomal protein S3[130].

Hippo-YAP/TAZ pathway: In the liver, there is evidence that Hippo-YAP/TAZ inactivation plays a role in fibrosis, hepatocarcinogenesis, and tumor behavior. More detailed information on this factor is presented in a recent review by Moon *et al*[131], with viral contributions to the Hippo-YAP/TAZ pathway summarized in Figure 3.

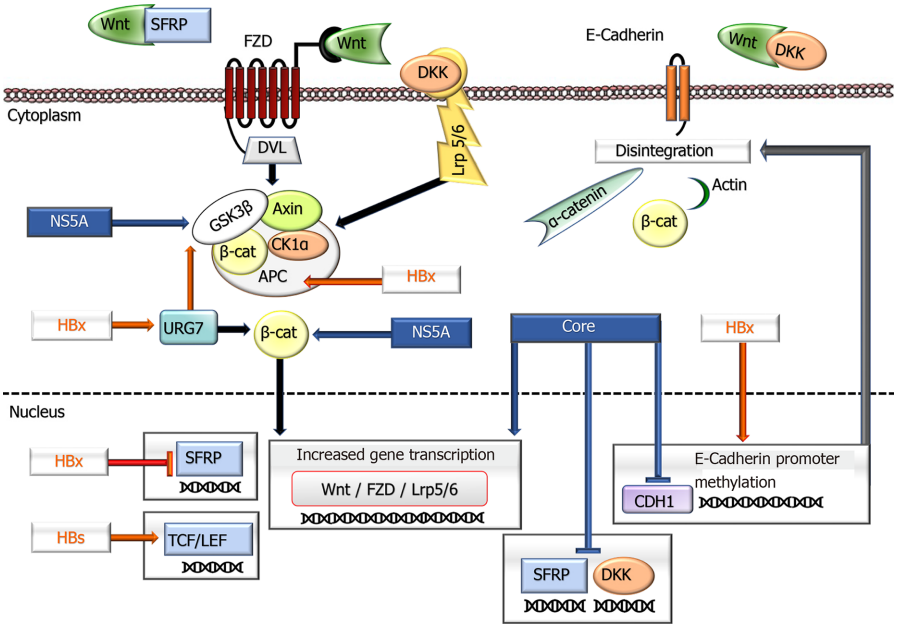

Figure 1 A schematic overview shows the impacts of hepatitis B virus and hepatitis C virus proteins in the Wnt signaling pathway. In an inactive state, cytoplasmic β-Catenin interacts with a multiprotein degradation complex comprised of CK1a, APC, GSK3β, and Axin, and following phosphorylation, is targeted for proteasome-dependent degradation. On binding Wnt ligands to FZD and LRP5/6 receptors, the scaffolding protein DVL is recruited to the membrane and phosphorylates GSK3β leading to the disassembly of the β-Catenin destruction complex. This event results in the rescue of β-Catenin from proteasomal degradation leading to its accumulation in the cytoplasm and eventually allowing its translocation to the nucleus. Consequently, β-Catenin activates the transcription of target genes through interaction with TCF and LEF family members. Wnt signaling is regulated by secreted proteins, including SFRPs and DKKs, which inhibit Wnt signaling by binding to FZD and LRP5/6 receptors, respectively. Independent of its transcriptional activity, β-Catenin, forming a complex with E-cadherin, also facilitates cellular junctions between cells. The disintegration of E-cadherin production causes the dissociation of the complex and subsequent internalization of β-Catenin, ending with activation of its target genes. Hepatitis B virus and hepatitis C virus proteins deregulate the expression of various components of the Wnt/β-Catenin pathway and contribute to tumor development and behavior. APC: Adenomatous polyposis coli; CK1: Casein kinase 1a; DKK: Dickkopf family of proteins; DVL: Disheveled segment polarity protein; FZD: Frizzled family of the receptor; GSK3b: Glycogen synthase kinase–3b; LEF: Lymphoid enhancing factor; Lrp5/6: LDL receptor-related protein 5/6; SFRPs: Secreted frizzled-related protein; TCF: DNA-bound T-cell factor; ⊥: Inhibition.

The primary region of the Hippo pathway, which is considered a critical tumor suppressor, consists of a protein complex. If the Hippo pathway is inactive or suppressed, YAP and TAZ are translocated to the nucleus and regulate the activation of transcription factors that play a role in cell proliferation, survival, miR processing, metastasis development, and maintaining stem cell continuity. Some studies have revealed that HBx expression in HCC tissues correlates with both the miR level and immunohistochemical nuclear expression of YAP[132,133] and its relationship with the cyclic adenosine monophosphate response element binding protein CREB pathway has been revealed[132]. In subsequent studies, there were also data demonstrating that HBx exerts its effect on p53 and ubiquitination of histone H2B, which plays a role in transcription control, through upregulation of FOX-1A and male-specific lethal 2 (MSL2), a ubiquitin E3 Ligase[134]. HBx also increases in YAP 1 by using NEDD with the E3 Ligase HDM2 to protect against ubiquitination and degradation[135]. In HBV-HCC cases, it has been shown that the c-terminal truncated middle surface protein of HBV, which is integrated into 30% of the host genome, increases TAZ activation by suppressing miR338-3p, promoting carcinogenesis[136]. Although these data on preS2, whose role in carcinogenesis has not been fully elucidated, are valuable, further studies are needed to address the effects of HBV on this pathway.

Angiogenesis pathways: In HCC, antitumor cell therapies, such as chemotherapy, are unsuccessful due to tumor cell heterogeneity. This has led to the application of new treatment options targeting relatively stable vascular cells in recent years. Currently, agents targeting angiogenesis are being used in the treatment of HCC. Vascular endothelial growth factor (VEGF) appears to be an important angiogenic factor in HBV-associated hepatocarcinogenesis. Together with VEGF in experimentally induced HBV-HCC mice, the increase in its expression supports this view[137]. In tumor tissues from patients with HBV-HCC, VEGF was also found to be upregulated, together with COX-2, and its expression correlates with microvessel density, which is a marker of angiogenesis[138]. In HBV-HCC, the primary inducer of VEGF expression is

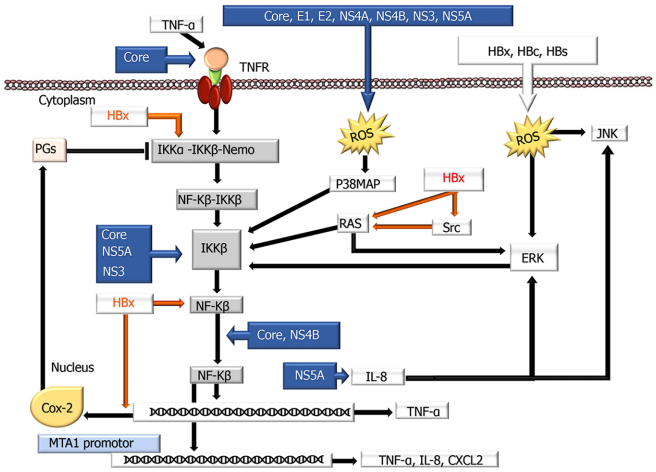

Figure 2 A schematic overview showing the influences of hepatitis B virus and hepatitis C virus proteins on the nuclear factor kappa-B signaling pathway. Nuclear factor kappa-B (NF-κB) normally localizes to the cytoplasm and binds to members of the inhibitory IκB family (IκBα, IκBβ, p105, and p100) of proteins, blocking the nuclear translocation of NF-κB. Therefore, deregulation of the IκB family is required for NF-κB to be translocated into the nucleus. Hepatitis B virus and hepatitis C virus use different mechanisms to modulate these transduction pathways by modulating NF-κB proteins activation, interaction with cellular proteins, interaction with other signaling cascades, and ER stress induction. COX-2: Cyclooxygenase-2; ERK: Extracellular signal-regulated kinase; IKK: IκB kinase; IL: Interleukin; JNK: c-Jun N-terminal kinase; p38 MAPK: p38 Mitogen-activated protein kinase; PG: Prostaglandin; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-α; TNFR: Tumor necrosis factor receptor; ⊥: Inhibition.

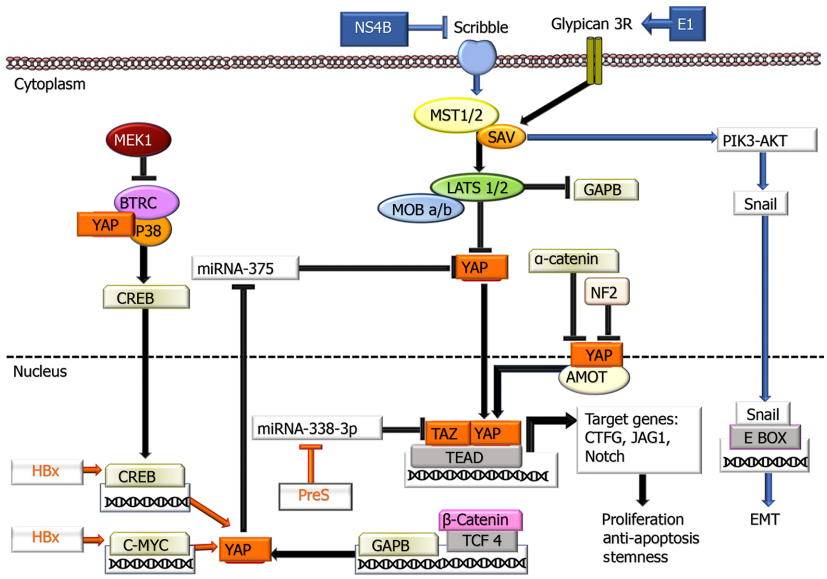

Figure 3 Involvement of hepatitis B virus and hepatitis C virus proteins in the Hippo-Make-TAZ signaling pathway. In the cytoplasm, YAP/TAZ proteins are inactivated by phosphorylation leading to their cytoplasmic retention. When YAP/TAZ is dephosphorylated, they can translocate into the nucleus and activate the transcription of their target genes through the interaction with the TEA domain transcription factor Scalloped transcription factors. Additionally, YAP stabilizes CREB through interacting with p38MAPK and beta-transducin repeat containing E3 ubiquitin protein ligase. MEK1 also inhibits the latter. On the other hand, GABP is negatively regulated by the Hippo signaling pathway. AMOT: Actin-associated protein angiomotin; BTRC: Beta-transducin repeat containing E3 ubiquitin protein ligase; CREB: cAMP response element-binding protein; LATS1/2: Large tumor suppressor kinase 1 and 2; MST1/2: Mammalian sterile 20-like kinase 1 and 2; P38 MAPK: P38 mitogen-activated protein kinase; NF2: Neurofibromin 2; SAV1: The adaptor proteins Salvador 1; Scribble: A basolateral polarity factor; TEAD: TEA domain transcription factor Scalloped; TCF4: Transcription factor 4; ⊥: Inhibition.

HBx. This protein increases VEGF expression in multiple ways in transfected cells and other cell cultures by stabilizing HIF-α or inducing mTOR and IKKβ[139]. In addition to VEGF, it also participates in angiogenesis by promoting increased expression and secretion of angiopoietin-2 (Ang-2) in liver tissue through activation of MAPK[139, 140]. HBx may also contribute to HCC angiogenesis through the upregulation of MMPs that promote angiogenesis by disrupting the basement membrane and other extracellular matrix components and allowing endothelial cells to migrate into the surrounding tissue. The correlation between HBx expression and the regulation of

MMP-2, MMP-9, MMP-14, and MMP protein levels and activities has been demonstrated[141]. It has also been reported that HBx contributes to angiogenesis in HCC by upregulating endothelin by activating PIK/AKT and downregulating lethal 7 by STAT activation[142]. HBx induces angiogenesis by increasing the expression of the metastasis-associated protein 1 (MTA1) coregulator through NF-κB signaling and by downregulating mammary serine protease inhibitor (Maspin)[141,142].

The Pre-S protein has also been reported to enhance VEGF expression, thereby increasing the angiogenic environment produced by the virus[139].

Integrins: The integrin family (ITGs) consists of cell-surface glycoprotein receptors composed of 14a and 8b subunits found in at least 20 species. The combination of these subunits leads to the emergence of more than 100 integrin heterodimers, resulting in a diversity of receptor-ligand combinations that can produce different effects specific to cell adhesion, which play important roles in the invasion and metastatic properties of tumor cells[143,144]. ITGs play two important roles in cancer development and progression: they mediate uncontrolled cell growth and differentiation by transmitting signals from the ECM into the cell and facilitating the invasive properties of tumor cells by changing the content of the surrounding matrix. However, the roles of ITGs in HCC, as in other cancers, are not easy to determine due to the complexity of their structures and functions and require further investigation. Despite the complexity of the functions of ITG, while ITGβ can act as a receptor for collagen, fibronectin, and laminin, ITGβ4 acts solely on laminin by binding with ITGα6[143]. Laminin-induced a6b4 may play a role in tumor formation and progression by affecting multiple signaling pathways, including p53, Ras, RhoA, and epidermal growth factor receptor family, to activate signaling pathways involved in tumorigenesis and metastasis, including PI3K, AKT, and MAPK signaling[144]. In HCC, there is an increase in the expression of some subunits of ITGs (α1, α2, α3, α6, and β1), especially at the tumor margin. Among these, decreased expression of ITG5β1, a negative regulator of fibronectin signal transmission, in poorly differentiated tumors with high metastatic capacity is a finding that supports integrins having differential roles in HCC. The results of several studies have shown that integrin α6β4 plays a role in HCC independent of the differences among hepatitis virus types[143]. More recently, Kim *et al*[144] observed that the levels of ITGa6, a laminin receptor, were higher in patients and animals with HBV-HCC than in other groups, including HCV-HCC, and this was found to be associated with early migration and invasion of tumor cells. In particular, HBx has been found to be involved in the expression of this glycoprotein, and its suppression reduces the metastatic properties of tumor cells. It has also been indicated that the key signaling molecule between ITGa6 and HBx is the p53 tumor suppressor. Therefore, the use of ITGa6 as a therapeutic target has been suggested[144]. However, the relationships of integrins with other HBV proteins during carcinogenesis in HCC remain to be elucidated.

The farnesoid X receptor: The farnesoid X receptor (FXR), a member of the nuclear receptor family, primarily stimulates bile excretion by suppressing the import and synthesis of bile acids into hepatocytes. However, the protective effect of FXR in hepatocytes is not limited to preventing the toxicity of bile acids but also involves inhibition of lipogenesis and stimulation of insulin sensitivity[145]. Moreover, it enhances EMT effects induced by TGF-β. After being experimentally determined to be an initiator of liver regeneration, FXR has also been found to be involved in HCC carcinogenesis related to chronic liver injury[146]. FXR expression is significantly lower in the livers of patients with HCC. In Huh7 cell lines, Niu *et al*[147] demonstrated that silencing FXR facilitates the growth, invasion, and metastatic properties of cancer cells. Parallel to this finding in $FXR^{-/-}$ mice, the cell cycle-associated proteins CyclinD1 and CyclinE1 were significantly increased. In brief, recent findings suggest that alterations in FXR might contribute to the development of HCC. Regarding HBV-HCC, limited data are available on the role of viruses in FXR expression. It has been demonstrated that HBx can activate FXR signaling, supporting its role through this nuclear receptor in hepatocellular carcinogenesis[147].

ROLE OF HCV IN HEPATOCARCINOGENESIS

HCV-induced epigenetic dysregulation

Unlike HBV, HCV, which does not integrate into the host genome, may play an important role in carcinogenesis and tumor behavior by creating epigenetic disorders

[148,149].

DNA methylation: Since HCV viral proteins can be found in the nucleus, they can generate nuclear signals in the host DNA[150,151]. The finding that the core protein significantly increases the expression of DNMT-1 and histone deacetylase HDAC1 suggests that it is capable of epigenetically silencing tumor suppressor gene expression that prevents tumor growth and progression[152]. This protein causes EMT induction and disruption of Wnt/β-Catenin signaling by suppressing SFRP[152,153]. The effects of HCV on changes in the methylation of genes, including APC, p73, p14, and OGMT, suggest that it may play a role in epigenetic silencing in malignant transformation[154, 155].

Histone modifications: Detection of viral-mediated acetylation of lysine 27 position histone 3 (H3K27Ac) in HCV-infected liver tissue suggests an effect of HCV on the disease through histone deacetylation[156,157]. H3K27Ac separates active from inactive/poised enhancer elements, promoting the transcription of associated genes, and is considered an activation mark during developmental states[158]. Moreover, the correlation between HCV-induced genome-wide H3K27Ac changes and the expression of genes at risk of developing cancer supports this virus's involvement in carcinogenesis through histone modification[156]. Another histone in HCV-mediated acetylation in carcinogenesis is histone H3 Lysine 9 (H3K9Ac), which shows parallel findings with H3K27Ac[159]. The fact that these epigenetic changes create a memory, or footprint, has been attributed to their detection persisting even after viral therapy [159,160]. Indeed, the presence of this epigenetic footprint is associated with aggressive tumor behavior in HCV-HCC cases, as well as increased cancer-risk gene expression after treatment in both experimental studies and patients with HCV hepatitis[156,159,161]. The persistence of the HCV-specific epigenetic footprint of 65 oncogenes has been detected both in the fibrotic liver of patients with cured HCV and in the liver of HCV-cured animals[156]. In addition, a fibrosis-related footprint of 1693 cancer-risk genes was observed in a study group including patients with fibrotic liver of HCV, and dysregulation of subgroups of these fibrosis-related epigenetic footprint genes have been defined as prognostic epigenetic signatures and may be useful in determining cancer risk[157]. An attempt was made to identify new treatments that could remove these footprints with various epidrugs[162].

miRs in HCV: Similar to HBV, HCV alters miR expression in a way that affects liver carcinogenesis[163-165]. miR-19a, miR-135-5p, miR-146a-5p, and miR-122 are also impaired by HCV infection and are associated with HCC development[165-167].

HCV and cellular signaling pathways in hepatocarcinogenesis

Wnt/β-Catenin pathway: In HCV-HCC, the frequency of *CTNNB1* mutations is approximately 26%, and this rate is significantly higher than that in either HBV-HCC (12%) or nonviral HCC (21%)[168-170]. Parallel to this finding, experimental studies have shown that HCV infection leads to *CTNNB1* mutation. It has been suggested that the NS3 protein of HCV may contribute to oncogenic transformation by disrupting DNA repair mechanisms, leading to *CTTNB1* mutation[171]. It should be noted that these data are very striking for a virus that does not exhibit DNA integration, and further studies are warranted to determine causal relationships. However, the effect of HCV is not limited to the *CTNNB1* mutation, and HCV-associated proteins also participate in the activation of Wnt/β-Catenin signaling[160]. The core protein is one of them. In particular, by regulating the hepatocyte transcription factor in the nucleus, the core protein can activate this pathway[172]. The core protein also induces the FZD receptor and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), supporting their activities by inhibiting antagonists, such as FZD-related protein 2 and Dickkopf 1 (DDK1)[173-176]. In the early phase of HCV infection, DDK1 inhibition plays a role in epigenetic silencing of the promoters by enabling the recruitment of DNA methyltransferase 1 and histone deacetylase[175]. In addition, it contributes to the inhibition of β-Catenin sequestration by hypermethylation of the gene promoter of E-Cadherin (CDH1)[174].

On the other hand, NS5A, one of the proteins involved in the HCV replication complex, is known to stabilize GSK3b both by direct binding and indirect inhibition through the PIK3-AKT pathway, leading to activation of Wnt/β-Catenin signaling [172]. There is also evidence that HCV, similar to HBV, activates this pathway through its effects on miRs. The effect of HCV on the Wnt/β-Catenin pathway is summarized in Figure 1.

NF-κB pathway: In the liver, the role of NF-κB in inflammation, fibrosis, carcinogenesis, and tumor progression has been demonstrated in HCV-HCC. HCV may have different effects (both activator and inhibitor) on this pathway[123]. In previous studies, it has been reported that NF-κB is overexpressed in patients with HCV[177]. For instance, core proteins can induce the TNF receptor (TNFR), which plays a key role in the activation of this pathway, by direct induction or by mimicking proinflammatory cytokines, such as TNF-α[178,179]. This protein can also stimulate Th-17 cells that produce cytokines that stimulate CD161, IL-17A, IL-17F, IL-21, and IL-22 on TNFR, enabling NF-κB activation[179-182]. There is evidence that E1 and E2 proteins also increase TNF-α secretion[183]. In contrast, recent experimental studies have observed that HCV can downregulate this pathway by activating several genes that suppress NF-κB. The NS3 and NS5B proteins suppress NF-κB activation by TNF-α [184]. Considering the important role of inflammation and oxidative stress in liver diseases, it is not surprising that core E1, E2, NS3, NS4A, NS4B, and NS5A induce oxidative stress to increase NF-κB, and these signals, in turn, induce ROS production through mitochondrial effects[124,185]. Paracha *et al*[186] demonstrated that core, NS3, and NS5A proteins are effective in promoting Ca^{++} release from mitochondria. In addition, ROS induced by viral proteins activate phosphorylation of extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38 MAPK), and c-Jun N-terminal kinase (JNK), which then promote NF-κB activation. Subsequently, activated NF-κB induces the expression of many genes, such as cyclooxygenase-2 (COX-2) and IL-8, by nuclear translocation. Chen *et al*[187] observed that the NS5A protein activates the NF-κB pathway and increases COX-2 expression by increasing ERK and JNK phosphorylation by inducing IL-8 production. On the other hand, COX-2 inhibits NF-κB activity by inhibiting IKK by bypassing the production of prostaglandins J2, A2, and A1. The role of HCV in this pathway is summarized in Figure 2.

Hippo-YAP/TAZ pathway: Similar to HBV, studies related to the Hippo-YAP-1 pathway are few, and most of them are experimental in HCV-HCC. The contribution of HCV to this pathway is presented in Figure 3. The HCV NS5B protein has been shown to play a role in EMT by inactivating the Hippo signaling pathway, upregulating Snail activity, and enabling PIK3/AKT activation[188]. In a few studies, there is evidence that the HCV E2 protein can mimic CD81, the major binding ligand for glypican 3. In this way, interestingly, it reduces Hippo activation and decreases YAP, attenuating proliferation[189]. Considering that CD81 is the entry route of HCV, it is concluded that due to the loss of CD81 in early carcinogenesis, this feature enables tumor cells to resist HCV during early HCC development, contributing to the clonal expansion of neoplastic cells compared to nontumor cells. Therefore, examining the possible effects of both factors on the Hippo pathway in carcinogenesis will enable us to determine whether this pathway represents a target for HCC therapy.

Angiogenesis pathways: Although various components of HCV have been reported to influence hepatocarcinogenesis, among them, the core protein has been reported to have the strongest potential associations with angiogenesis. It enhances the expression of angiogenic factors, including VEGF and Ang-2, by activating various growth factor signaling pathways, such as MAPK, PIK3, and JNK[190-193]. Some studies have reported that the core protein increases VEGF through androgen receptor-mediated transcription by activating STAT3[194]. On the other hand, despite the same correlation of androgen and VEGF expression in other studies, no increase in STAT3 was observed[195]. It has been suggested that this may be due to experimental methodological differences, such as the use of different genotypes of the core protein. Similarly, inconsistent results were obtained regarding the interaction of the core protein with the PIK3 and MAPK pathways during the induction of VEGF expression [196-198]. Recently, Shao *et al*[195] demonstrated that the HCV core protein's proangiogenic activity is dose-dependent and that the mechanism involves an increase in VEGF expression through activator protein-1 activation. The core protein can also induce angiogenesis by increasing the expression of endoglin (CD105), which plays an important role in TGF-β signaling[199].

After the apelin system (APJ) was shown to have a role in HCV-HCC during carcinogenesis progression in recent years, the relationship of this system with angiogenesis was revealed[200]. Although more research is needed to better understand apelin's role in HCC, Cabiati *et al*[201] recently demonstrated that higher expression of this angiogenic agent in patients with HCV-HCC is consistent with pathological staging and emphasized that APJ could be considered important for developing therapeutic targets that identify new pathways for cancer treatment.

In the study of gene expression for secreted proteins in HCV-infected hepatoma cells by applying microarray analysis, it was found that HCV exerts a proangiogenic effect by inducing the EGFR-ERK signaling pathway[202].

FXR: Although there are several studies on the role of FXR in the pathogenesis of HCV hepatitis, further studies are needed to understand its role in HCV-HCC.

ROLE OF HBV AND HCV IN INFLAMMATION AND CARCINOGENESIS

At the onset of inflammation, hepatocyte differentiation and proliferation after exposure to acute injury or microbe patterns or danger-related molecular models (DAMPs) are directed toward liver repair[203]. However, persistent inflammation caused by cellular damage and loss triggers the immune response, leading to the development of HCC. Therefore, inflammation plays a very important role in hepatocarcinogenesis, similar to other types of cancer. The autoamplification cycle created by proinflammatory pathways induced by the release of DAMPs in necroinflammation, defined as cell death caused by the immune response, promotes hepatocarcinogenesis by disrupting genetic stability during DNA degradation[125]. In addition, during hepatocarcinogenesis, disruption of the immune system and release of cytokines that cause immune suppression (IL-10, IL-13, and TGF-β) promote malignant transformation by preventing the elimination of atypical cells by both innate and acquired immunity[143].

Viral inflammation plays a significant role in the development of both HBV-HCC and HCV-HCC. In this section, the effects of viral inflammation on carcinogenesis will be discussed separately under three main headings, each of which has a significant role in HCC development.

Inflammasome

Inflammasomes are important components of the innate immune system that regulate caspase-1 activation and inflammation and have recently been proposed as therapeutic targets for many inflammatory diseases. They consist of large protein complexes that initiate downstream signaling, resulting in the release of type I interferons and proinflammatory cytokines through model recognition receptors (PRRs) that are stimulated by pathogen-related molecular models and DAMPs [125]. Several PRR families are important components in the inflammasome complex, including the nucleotide-binding domain, leucine-rich repeat proteins (also known as NOD-like receptors, NLRs), and melanoma (AIM)-like receptors (also known as ALRs)[204]. After stimulation, the relevant inflammasome PRR (for instance, NLRP3 in hepatocytes) oligomerizes to become a caspase-1 activator, leading to cleavage of proinflammatory IL-1 cytokines into IL-1β and IL-18 and subsequent pyroptosis[205] (Figure 4).

Different findings have been reported on the participation of inflammasomes in oncogenesis in the liver and their interaction with viruses in the development of HCC [206]. Some studies have demonstrated that the NLRP3 inflammasome is significantly reduced in tumors compared to nontumor tissues[207]. It also induces IL-18, resulting in NK cell-mediated suppression of colorectal cancer metastasis to the liver[208]. In addition, 17β-estradiol (E2), which plays a protective role in hepatocarcinogenesis, decreases tumor progression by increasing the NLRP3 inflammasome by the E2/ERβ/MAPK signaling pathway[209]. These findings support the NLRP3 inflammasome's preventive role in HCC. In contrast, it has been observed that during hypoxia, HMGB1, through activation of NLRP3, enhances caspase-1, IL-1β, and IL-18 to promote tumor invasion[210]. HCV activates NLRP3, leading to its accumulation in lipid droplets, where it coordinates with sterol-regulatory-element-binding proteins to promote liver disease[211]. HCV also induces hepatic macrophages to produce IL-1β through the NLRP3 inflammasome, leading to disease progression[212].

Another inflammasome, AIM2, induces IL-18 expression in human Kupffer cells, which stimulates NK cells to produce interferon (IFN)-γ in the regulation of innate immunity[213]. In patients with HBV, increased AIM2 expression was observed in the high HBV replication group compared to the low HBV replication group, with high AIM2 Levels being positively associated with IL-1β and IL-18 expression, suggesting that this inflammasome may be involved in viral elimination[214]. However, another finding indicated that AIM2 prevents the recognition of DDS expressed by HBV to assist in immune evasion[213]. These data also demonstrate that inflammasomes are differentially regulated by HBV proteins (Figure 4).

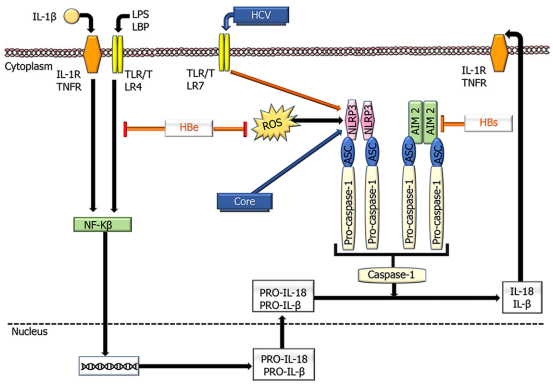

Figure 4 Schematic overview showing the effects of hepatitis B virus and hepatitis C virus proteins on the functioning of NLR family pyrin domain containing 3 and absent in melanoma 2 inflammasomes. Inflammasome activation is defined by oligomerization of NLR family pyrin domain containing 3 and absent in melanoma 2, which recruits apoptosis-associated speck like proteins and pro-caspase- 1, leading to caspase-1 activation and subsequent conversion of pro-IL- 1β into active IL-1β. HCV: Hepatitis C virus; ASC: Apoptosis-associated speck-like protein containing a CARD; AIM2; Absent in melanoma 2; IL: Interleukin; LPS; Lipopolysaccharides; LBP: Lipopolysaccharide binding protein; NLRP3: NLR family pyrin domain containing 3; TLR: Toll-like receptor; TNFR: TNF receptor; ⊥ : Inhibition.

In the liver, Kupffer cells play a critical role in IL-β and IL-18 release in the inflammasome-mediated inflammatory response. However, there are different reports regarding IL-1β inhibiting HBV infection in liver cells. For instance, priming with IL-1β reduces host cell susceptibility to HBV infection through activation-induced cytidine deaminase[215] and oxidative stress[216]. Although HCV-infected monocytes induce IL-18 through inflammasomes that activate IFN-γ-producing NK cells, patients with chronic HCV infection exhibit reduced monocyte function and low IFN-γ levels [217]. These findings are explained by changes in membrane protein composition on monocytes derived from chronic HCV patients who present depleted levels of IFN-γ due to decreased numbers of CD14+ monocytes. Taken together, these findings show that inflammasomes derived from monocytes, NK cells, and macrophage-derived inflammasomes perform differential functions in hepatitis.

However, all of these data necessitate further investigations to decipher the role of inflammasomes in HCC.

NF-κB and STAT3 signaling in inflammation-related oncogenesis

The effect of HBV and HCV on the inflammation-mediated contribution of NF-κB to viral carcinogenesis in HCC has been discussed above.

STAT3 signaling plays an important role in the contribution of inflammation to the development and formation of HCC[143,218]. This pathway can be activated by many cytokines and growth factors, including IL-6, TNF, the EGF family, and hepatocyte growth factor[219,220]. As indicated by Wu *et al*[143], STAT3 activation leads to strong inhibition of SHP phosphatases and suppressor of cytokine signaling 3, which is inhibited in tumor cells. The accumulation of oxidative stress in both HBV and HCV infection can activate STAT3 by inducing JNK expression, allowing phosphorylation of a critical tyrosine kinase residue (Tyr705). Therefore, viral inflammation causes overexpression of proinflammatory cytokines, including IL-6, IL-10, IL-11, and TGF-α, which regulate the liver microenvironment to support oncogenic conditions, such as inhibition of apoptosis. The multiple roles of STAT3 activation in proliferation and anti-apoptosis (Cyclin D, Bcl-xL, Bcl-2, Caspase), migration and invasion (MMP-4, MMP-9, Slug, Twist), angiogenesis (VEGF, bFGF, HIF-α), and cancer stemness (CD131, NANOG, Notch) make its inhibition an attractive therapeutic target[218]. More recently, in an elegant study, Qin *et al*[221] demonstrated that in patients with advanced HBV-HCC, the use of icaritin, a small molecule that displays anticancer activities through the IL-6/JAK/STAT3 pathway, could be used as an alternative immune-modulatory regimen to treat advanced HCC patients with poor prognosis.

Immune escape

Hepatocytes have the capacity to develop a tolerogenic immune milieu in which innate and acquired immunity play important roles in preventing permanent damage [222]. Unfortunately, these mechanisms also allow tumor cells to escape from the immune system during oncogenesis. Indeed, the reduction in antigen presentation activity, evidenced by decreased expression of HLA class I molecules and suppression

of CD8+ T cells with an increasing number of Tregs, contribute to oncogenesis[223-225]. Similar findings were also noted for NK T cells, myeloid-derived suppressor cells, tumor-associated macrophages (TAMs), and decreased CD4+ T cells[226,227]. In this context, the transition between proinflammatory (M1) and anti-inflammatory (M2) phenotypes of macrophages is very important. The transformation of macrophages into the M2 phenotype, which is effective in exhibiting anti-inflammatory functions by releasing Th2 cytokines (IL-4, IL-10, and IL-13), favors hepatocarcinogenesis[125,228]. In addition, it has been reported that HSCs exhibiting loss of p53 may contribute to the increase in macrophages with the M2 phenotype[143]. In HCC, positive correlations among the increase in anti-inflammatory cytokines, distant metastasis, and poor prognosis demonstrate that immune escape during inflammation promotes carcinogenesis and tumor behavior[229]. Moreover, inflammatory cells and cytokines demonstrably support cancer stem cells by the IL-6/STAT3 pathway. In vitro, the release of IL-6 may induce the expansion of CD133-positive cancer progenitor cells [230]. The IL-6/STAT3 paracrine signaling pathway from TAMs also triggers the proliferation of cancer progenitor cells to facilitate hepatocarcinogenesis[222]. Recently, the results of a study by Song *et al*[231] delineated that HBV/HCV-related HCC includes new types of immune cells that may play a role in immune escape and highlighted the potential of this condition to play a role in HCC formation and the progression of viruses in uncovering new targets for tumor therapy.

AUTOPHAGY IN HBV AND HCV RELATED HCC

Autophagy is an evolutionarily conserved cellular pathway in which long-lived cytoplasmic proteins and organelles are engulfed into double-membrane vesicles known as autophagosomes that subsequently fuse with lysosomes and are regulated by a series of autophagy-related genes (Atgs)[232]. Atg5, Atg7, and Beclin 1 (BECN1) are essential genes in this process, and silencing any of these genes leads to blockage of autophagy. Previous studies suggest that autophagy acts as a double-edged sword in carcinogenesis and tumor behavior[233]. It can function as a tumor suppressor in the early stage of cancer development by inhibiting inflammation and promoting genomic stability. In contrast, autophagy confers a survival advantage to tumor cells by supplying nutrients and energy and promoting angiogenesis. Many studies have evidenced the role of autophagy in HCC initiation and development. The results indicate that autophagy plays a suppressive role in the onset of HCC development and acts as a promoter after tumor development in advanced stages. For more detailed information on this topic, the elegant reviews by Cui *et al*[234] and Lee *et al*[235] are recommended.

Recent studies have shown that HBV induces autophagy, particularly with HBx and HBs proteins, to improve its survival and replication[236]. However, the role of autophagy in HBV-associated tumorigenesis is not entirely clarified. Autophagy downregulated HBV-HCC in both humans and mouse models[237]. HBV-induced liver cell neoplasia progression stimulated in BECN1-null mice suggests that increased malignant transformation risk is inversely correlated with autophagy induction[238]. In HBV-HCC tissues, the expression of BECN1 and Atg5 is decreased compared to that in chronic hepatitis[239].

Similarly, although the exact mechanisms of downregulation of autophagy in HBV-HCC remain unclear, it is suggested that autophagy can increase the antitumor immune response[240], induce cell death[241], and lead to oncogenic microRNA degradation[242]. These results imply that autophagy, which plays a tumor-suppressive role in hepatocarcinogenesis, is inhibited in HBV-associated tumorigenesis. However, the mechanism by which high autophagy during HBV infection shifts to low autophagy in HBV-related tumorigenesis remains to be elucidated.

HCV infection can also promote inflammation by leading to the activation of inflammasomes and the production of proinflammatory cytokines, including IL-1α and IL-1β, thereby promoting fibrosis carcinogenesis[212]. NLRP3 inflammasome activation through calcium mobilization linked to phospholipase-C through HCV core protein is defined during progressive liver disease, and HCC is also noted[243]. Together with the finding that this activation can be counteracted by autophagy activation under certain circumstances, these data support HCV disease's contribution to progression by autophagy[244]. HCV-induced endoplasmic reticulum ER stress is evidenced by the observation of increased elevation of ER stress markers in HCV-related cirrhosis [245]. Moreover, in HCV cell cultures, Aydın *et al*[246] observed that excessive ER stress activates NRF2-mediated autophagy switching to promote cell survival.

Considering that NRF2 plays a role in the development of HCC through the accumulation of p62, HCV may also contribute to carcinogenesis through autophagy regulation mechanisms[247]. Recently, the contribution of immunity-related GTPases (IRGs), a family of IFN-inducible GTPases, to autophagy has been implicated[248]. IRGM is a critical negative regulator of NLRP3 inflammasome activation by interacting with NLRP3 and ASC and subsequently inhibiting inflammasome assembly[249]. A recent study pointed out that HCV-induced IRGM-mediated phosphorylation of ULK1 induces autophagy[250]. It is proposed that IRGM-mediated autophagy after HCV infection might contribute to the tumor-promoting effects of HCV.

Currently, further studies are needed to fully understand the effect of HCV on carcinogenesis and tumor behavior through autophagy.

Finally, it should also be noted that the association of autophagy with the pathways mentioned above involved in HCC development also contributes to both HBV and HCV-associated carcinogenesis.

MICROBIOTA IN HBV AND HCV RELATED HCC

Although its role in HCC is not fully clarified, there is evidence that the intestinal flora is involved in carcinogenesis[251-253]. For instance, a human study has shown that *Helicobacter hepaticus* is present in the livers of patients with HCC compared to the livers of controls without carcinoma[251]. A remarkable observation is the absence of this microorganism in HBV-HCC and HCV-HCC, which necessitates further studies to be clarified entirely. On the other hand, in an elegant study, Huang *et al*[253] found that *Bacteroides, Lachnospiraceae incertae sedis*, and *Clostridium XIVa* were enriched in HBV-HCC patients with a high tumor burden. Therefore, extensive research in this context could reveal more comprehensive information about the use of microbiota changes as a treatment target.

CONCLUSION

Despite extensive studies on its development and behavior, HCC remains a major health problem worldwide. The main therapeutic strategies that are currently being used in the treatment of HCC include angiogenesis inhibitors, multikinase inhibitors, pathway-targeted therapies (especially the Wnt-β-Catenin and NF-κB pathways), immunotargeting (for immune escape), inflammasome-targeting therapies, and immunotherapy[143]. Compared to other common cancers, such as breast and colon cancers, the numerous variations caused by this tumor's very complex molecular profile constitute a critical limitation for clinical trials. Therefore, uncovering the molecular mechanisms associated with HCC development and tumor behavior is very significant for both decreasing tumor prevalence and identifying new treatment targets. In this context, it is crucial to clarify the effects of HBV and HCV on the molecular events involved in oncogenesis and prognosis due to their close relationship with HCC. Unfortunately, unlike other viruses, it is not possible to identify a single oncogene or mechanism in terms of carcinogenesis and progression. In contrast, complex mechanisms reflect concerted and cumulative effects of chronic inflammation-related alterations, modification of oncogenic pathways (especially tumor suppression, proliferation, apoptosis), and epigenetic dysregulation in response to both viruses. In addition, the integration of HBV into host DNA may also affect tumor development and behavior.

Therefore, further studies to characterize new mechanisms of HBV and HCV-associated carcinogenesis and tumor progression may reduce the prevalence of HCC and lead to the discovery of new treatment targets to overcome the grim prognosis of this disease.

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