REVIEW

Hepatitis B virus infection and the risk of hepatocellular carcinoma

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Abstract
Epidemiological studies have provided overwhelming evidence for a causal role of chronic hepatitis B virus (HBV) infection in the development of hepatocellular carcinoma (HCC). However, the pathogenesis of HBV infection and carcinogenesis of HBV-associated HCC are still elusive. This review will summarize the current knowledge on the mechanisms involved in HBV-related liver carcinogenesis. The role of HBV in tumor formation appears to be complex, and may involve both direct and indirect mechanisms. Integration of HBV DNA into the host genome occurs at early steps of clonal tumor expansion, and it has been shown to enhance the host chromosomal instability, leading to large inverted duplications, deletions and chromosomal translocations. It has been shown that the rate of chromosomal alterations is increased significantly in HBV-related tumors. Prolonged expression of the viral regulatory HBV x protein may contribute to regulating cellular transcription, protein degradation, proliferation, and apoptotic signaling pathways, and it plays a critical role in the development of hepatocellular carcinoma.

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Key words: Hepatocellular carcinoma; Hepatitis B virus infection; Hepatitis B virus genotypic variations; Hepatitis B virus x protein

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INTRODUCTION
Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and the third most common cause of cancer mortality.[1,2] This tumor, which arises from hepatocytes, is often associated with liver cirrhosis resulting from chronic liver diseases. Among the environmental risk factors, the prevalence of chronic hepatitis B and C virus infections is linked directly to the incidence of HCC. There is now evidence for persistence within the tumor cells of a low level HBV multiplication potential. Hepatitis B virus (HBV) DNA replicative molecules and covalently closed circular DNA (cccDNA) are detectable by polymerase chain reaction (PCR). Moreover, the association between HCC and HBV recurrence after liver transplantation, and the detection of cccDNA in HCC cells point toward the possibility of HBV replication in tumor cells. The latter could act as potential reservoirs for HBV recurrence, especially in patients who present with a recurrence of HCC.[3] So far, chronic and persistent infection with hepatitis B virus is a major risk factor for the development of HCC.

Globally, it is estimated that 350 million people are chronically infected with the HBV.[4] Approximately 25% of
chronically HBV-infected individuals will develop HCC[6]. Chronic carriers of HBV have up to a 30-fold increased risk of HCC[6]. In areas of high HBV endemicity, persons with cirrhosis have an approximately 16-fold higher risk of HCC than the inactive carriers, and a 3-fold higher risk for HCC than those with chronic hepatitis but without cirrhosis[7]. Although the mechanisms of oncogenesis of HBV remain obscure, several factors have been identified to be associated with a high risk of developing HCC among chronic hepatitis B (CHB) patients. HBV exerts its oncogenic potential through a multi-factorial process, which includes both indirect and direct mechanisms that likely act synergistically[8].

Hepatitis B virus genotypic variations and the risk of hepatocellular carcinoma

Specific genotypic variations in HBV have been associated with cirrhosis and HCC. These variations include, in particular, mutations in the pre-core region (Pre-C, A1896G inside the g structure of the genome), in the basal Core promoter (A1762T/G1764A), and in ORF's encoding PreS1/PreS2/S and Pre-C/C. There is an overlap between Pre-C or basic core promoter (BCP) mutations and genotypes, since these mutations appear to be more common in genotype C as compared to other genotypes[9]. The 1762T/G1764A double mutations (1762 A-to-T and 1764 G-to-A) in the BCP region were commonly found to be borne by HCC patients in some high-risk populations, and were thus suggested as potential biomarkers for hepatocarcinogenesis[10]. Comparison of HBV isolates from different studies indicates that the mutation rate of A1762T/G1764A is 64% for genotype C, 40% for genotype B and 35% for other genotypes[11]. Kusakabe et al[12] investigated a population-based cohort consisting of 19,393 subjects (middle aged or older) with a follow-up of over 13 years in Japan. They found that HBV mono-infected subjects with the A1762T/G1764A double mutation could be at high risk for HCC development during the natural course of HBV infection[13]. In addition, the 1753T/G-to-C/A mutations (1753-to-C/A/G) were also associated with the progression of liver disease[14]. Li et al[15] evaluated the roles of genetic variations of HBV in the development of HCC in Southern Guangxi China. Their study supported the hypothesis that both the 1762T/G1764A double mutations and the 1753V/1752V mutations were associated with increased risk for HCC. Fan et al[16] found that patients with higher viral load and genotype C had a higher incidence of 1762/1764 double mutations, and that Enhancer II and DRI were significantly more in the HCC group than in the CHB group, which may play an important role in HCC development via nucleotide substitution. The BCP mutations could affect the core promoter that regulates the expression of both HBsAg and the core protein, and this may be related to the higher rate of replication of genotype C. Substitutions in the BCP may increase genotype virulence by deregulating the transcription of pcARN/pgARN, increasing the risk of HCC in patients infected with genotype C[17]. Thus, the BCP overlaps with the X region of the HBV genome, and mutations in the amino acid sequence at positions 130 and 131 in this region have been proposed as prognostic markers for the development of liver cancer[18].

Viral genotype and the risk of hepatocellular carcinoma

The viral genotype is another factor that affects cancer risk. Genotype C has a higher risk of causing HCC than genotype B[14,15], and genotype D has a higher cancer risk than genotype A[16]. Compared to the Asian genotypes (B and C), the European genotypes (A and D) are less well established.

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Mutations in Pre-S have been reported in HCC cases compared to chronic or asymptomatic cases. These mutations, including deletions in Pre-S in the integrated HBV DNA, may impair the secretion of HBsAg, leading to increased endoplasmic reticulum and oxidative stress in hepatocytes. Truncated forms of Pre-S2 have also been shown to interact with cyclin A, a critical regulator of the cell division cycle, an observation that supports a role for Pre-S2 in hepatocyte hyperplasia and a likely role in the process of HBV-related tumorigenesis. Thus, deletions of Pre-S may contribute to hepatocarcinogenesis by several mechanisms.

Altogether, this combination of genomic mutations, and/or deletions, together with transcriptional and post-transcriptional regulations, will therefore allow the establishment of viral persistence, and the ongoing synthesis of HBV antigens.

**DNA METHYLATION AND THE RISK OF HEPATOCELLULAR CARCINOMA**

DNA methylation occurs in the early stage of cancer development, including HCC. Genomic hypomethylation increases chromosome instability while localized hypermethylation decreases tumor suppressor gene expression, thus increasing the risk of HCC development. Aberrant methylation of RASSF1A (Ras association domain family member 1) is thought to be an early event in the development of HCC. The process is catalyzed by DNA methyltransferases (DNMT). DNMT inhibitors directly repress tumor angiogenesis, indicating that epigenetic modifications mediated by DNMT are involved in the regulation of gene expression during tumor angiogenesis. Another significant link has been suggested between HCC development and the silencing by DNA hypermethylation of several tumor suppressor genes (TSGs). A number of TSGs, including p16, SOCS-1, APC, GSTP1 and E-cadherin, are silenced by DNA methylation in a large proportion of liver tumors, and this process often starts at the preneoplastic stage. In some reports, a higher rate of promoter methylation for specific genes, such as p16 and E-cadherin, has been observed in HBV-related tumors compared to nonviral tumors.

**HEPATITIS B VIRUS X PROTEIN AND THE RISK OF HEPATOCELLULAR CARCINOMA**

The hepatitis B virus x protein (HBx) protein is a 154 amino acid polypeptide with a molecular mass of about 17 kDa. HBx appears to play a critical role in the development of HCC. HBx is important for HBV replication and can regulate cellular transcription, protein degradation, proliferation, and apoptotic signaling pathways (reviewed by Bouchaud and Schneider). HBx protein does not bind directly to DNA, but rather acts on cellular promoters by protein-protein interactions and by modulating cytoplasmic signaling pathways. The cell cycle inhibition effect of HBx was validated through a liver regeneration experiment reported by Sidorkiewicz et al. Kuo et al. reported that HBx can downregulate Wnt/β-catenin expression and suppress cell growth by not only repressing cell proliferation, but also triggering cell apoptosis. Furthermore, Hsien et al. have found that HBx protein interacts with the tumor suppressor adenomatous polyposis coli to activate Wnt/β-catenin signaling. Wnt/β-catenin has been shown to up-regulate the epithelial cell adhesion molecule in HCC cells to promote tumor initiation and stemness. Thus HBx activation of Wnt/β-catenin may promote directly the transformation of liver cells into cancer initiating cells. A number of ways in which HBx protein may induce antiapoptotic effects have been described. The most important of these is the ability of HBx to inhibit p53-mediated apoptosis. Recent experiments have suggested that HBx protein may increase the expression of telomerase reverse transcriptase and telomerase activity, prolonging the lifespan of hepatocytes and contributing to malignant transformation. The protein also interferes with nucleotide excision repair through both p53-dependent and p53-independent mechanisms. Carboxyl-terminal truncated HBx protein loses its inhibitory effects on cell proliferation and pro-apoptotic properties, and it may enhance the protein’s ability to transform oncogenes. Dysregulation of IGFl-II enhances the proliferation and anti-apoptotic effects of oncogenes, resulting in uncontrolled cell growth. Another possible explanation for the anti-apoptotic effect of HBx protein involves the accumulation of the anti-apoptotic protein, survivin. Guo et al. found that Hep3B cells expressing HBx protein increased the levels of hepatoma upregulated protein (HURP) RNA and protein, and showed resistance to cisplatin-induced apoptosis. Knockdown of HURP in these cells reversed this effect. The anti-apoptotic effect of HBx protein was shown to require activation of the p38/mitogen activated protein kinase (MAPK) pathway. In addition, the expression of survivin was upregulated by HBx protein in an HURP-dependent manner. High levels of HURP favored the expression of the anti-apoptotic survivin in HBx-expressing cells. These results indicate that HBx protein activates the expression of HURP via the p38/MAPK pathway, culminating in the accumulation of survivin. In recent years, evidence has accumulated that HBx protein modulates the transcription of methyl transferases, causing regional hypermethylation of DNA that results in silencing of tumor suppressor genes, or global hypomethylation. This, in turn results in chromosomal instability, thereby playing a role in hepatocarcinogenesis.

The p16 INK4A gene is known as an abnormal tumor suppressor gene and critical cancer-related gene in human hepatocarcinogenesis. Several studies have shown that hypermethylation of the p16 INK4A promoter is an important early event in carcinogenesis. Zhu et al. found that HBx upregulates DNMT1 and DNMT3A expression at both the mRNA and protein levels, and that HBx represses p16 INK4A expression by inducing hypermethylation of
the p16\textsuperscript{INK4A} promoter. Moreover, HBx induces the hypermethylation of the p16\textsuperscript{INK4A} promoter through DNMT1 and DNMT3A. Regulation of DNMT1 and DNMT3A by HBx promotes the hypermethylation of the p16\textsuperscript{INK4A} promoter region.[40,41]

Among the activities of HBx, its trans-activation function may play a crucial role in hepatocarcinogenesis, because it is involved in the activation of a large number of signaling pathways and cellular genes that are involved in oncogenesis, proliferation and inflammation. For example, HBx transactivates a number of cellular promoters and enhancers containing binding sites for nuclear factor-kappa-B, activator protein 1 (AP-1), AP-2, cellular promoters of genes associated with cell proliferation such as IL-8, TNF, TGF-\beta, and epidermal growth factor receptor, and cytosolic signal transduction pathways including Src kinases, G\textsubscript{j}N-terminal kinase, J\textalpha{}K1/STAT and protein kinase, which have overlapping effects on cell proliferation and viability.[40,41]

CONCLUSION

The studies we have reviewed here illustrate that HBV constitutes a major environmental etiological factor for primary liver cancer in humans. It will therefore be important to analyze gene expression and proteome changes in a large series of samples from CHB at different stages, to identify suitable prognostic markers and therapeutic targets. Furthermore, detection of the viral genomes using sensitive, PCR-based, assays is mandatory to enable an accurate appraisal of their prevalence. Genomic alterations get. Furthermore, detection of the viral genomes using sensitive, PCR-based, assays is mandatory to enable an accurate appraisal of their prevalence. Genomic alterations and epigenetic factors like methylation-associated gene silencing may play an important role in the deregulation of cellular functions, leading to malignant transformation. A better understanding of the complex role of HBV in hepatocarcinogenesis will undoubtedly contribute to the improvement of the management of liver diseases induced by CHB.

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