

Key role of hepatitis B virus mutation in chronic hepatitis B development to hepatocellular carcinoma

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insertion and truncation mutation of *HBV* gene in 4 open reading frames (S, C, P, X), are closely associated with HCC pathogenesis. Some mutations accumulated during chronic HBV infection could be regarded as a biomarker to predict the occurrence of HCC. The detection of the mutations in clinical practice could be helpful for defining better preventive and therapeutic strategies and, moreover, predicting the progression of liver disease.

Key words: Hepatitis B virus; Mutations; Hepatocellular carcinoma; Carcinogenesis; Chronic hepatitis B

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Core tip: This mini review fully describes the relationship between hepatitis B virus (HBV) genome mutations in different regions with liver disease progression and development to hepatocellular carcinoma (HCC) according to the recent data of mutations in chronic hepatitis B patients. Accordingly, the HBV mutations, either in the preS or PreC or/and core promoter region, are significantly associated with HCC and could be regarded as a biomarker to predict the occurrence of HCC.

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Abstract

Chronic hepatitis B virus (HBV) infection is a major risk factor for hepatocellular carcinoma (HCC). The HBV mutations, which include point mutation, deletion,

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a medical problem and the main cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) worldwide. The major risk factor of HCC carcinogenesis is chronic HBV infection, especially in China. Other factors,

including products of HBV, HBV integration and mutation and host susceptibility, contribute to HBV-related HCC. At present, carcinogenesis in HBV infection is not well understood^[1]. The main contribution of HBV infection development to HCC is progressive stages of liver fibrosis and nonresolving inflammation^[2,3]. The HBV genome contains four partially overlapping open reading frames (ORFs) (preS/S, preC/C, P and X) which have diverse kinds of patterns of mutations. The mutations, including point mutation, deletion, insertion and truncation in 4 ORFs, are closely associated with HCC pathogenesis and liver disease progression^[4,5]. This mini review provides an overview of the recent data regarding development to HCC of HBV mutation in chronic hepatitis B patients.

S REGION GENE MUTATION

The S region of ORFs are composed of three translation start codons (AUG codons) coding the expression of three kinds of proteins: large (L), middle (M) and small (S). PreS1 region is unique for L protein. PreS2 region is the shared sequence with the M protein and the S region is seen in all three kinds of proteins. The L and S proteins are fundamental for virion formation and the M enhances the virion secretion efficiency^[6,7]. The S and M proteins are detected as hepatitis B s antigen (HBsAg). The dominant epitopes of HBsAg are the targets of neutralizing B cell responses, located in the "a" determinant (aa 124-147) in the major hydrophilic region^[8].

The relationship between S gene mutation and HCC were studied focusing on the preS region. HBV preS mutations are closely related to an increased risk of HCC. Both the single and combined mutations with the other region gene mutations may be predictive for hepatocarcinogenesis.

Qu *et al*^[9] found that T53C mutation, preS2 start codon mutations and preS deletions were related to HCC significantly in a study. The longitudinal study showed that the preS deletion mutations occurred during the long course of liver diseases, but not at the beginning of HBV infection.

Wang *et al*^[10] found that preS mutant large HBV surface antigens (LHBs) can initiate endoplasmic reticulum (ER) stress to induce oxidative DNA damage and genomic instability. PreS mutant LHBs can up-regulate cyclooxygenase-2 and cyclin A to induce cell cycle progression and proliferation of hepatocytes. Dysplasia of hepatocytes can be induced by preS mutants in transgenic mice. In a nested control study, the presence of preS mutants was closely associated with development to HCC in HBV carriers.

In an interesting recent study, Su *et al*^[11] observed that in a transgenic mice model, preS2 mutants induced ER stress-dependent and independent pathways, leading to oxidative DNA damage, genomic instability and transforming capabilities. In their study, the combined expression of HBx and preS2 mutant showed enhanced oncogenic effects in HCC development; however, the

concrete role of X protein (HBx) and preS2 mutant protein in HCC carcinogenesis is still to be clarified.

T53C, preS1 deletion, preS2 start codon mutation, C7A, A2962G, C2964A and C3116T in the preS region are significantly related to an increased risk of HCC^[5]. Furthermore, the effects of other HBV preS/S mutations in hepatocarcinogenesis are still limited.

PREC/C REGION GENE MUTATION

Mutations in the core promoter and precore regions of HBV lead to downregulation of hepatitis B e antigen (HBeAg). These mutations are related to chronic hepatitis, cirrhosis and HCC. C ORF of HBV genome encodes core protein and HBeAg^[12]. The core shell of HBV is an effective immune stimulator, activating an intense neutralizing immune response to foreign epitopes. Mutations in this region of the HBV genome focus in the region of basal core promoter (BCP) and PreC^[13].

T1762/A1764 double mutations in BCP is the most convincing association between HBV mutation and the development of HCC. The relationship between BCP double mutations and HCC were proved in two large prospective cohort studies^[14]. Moreover, V1753, T1766, A1768 in BCP and T1653 mutations in box- α of Enhancer II have been shown to be associated with the development of HCC in several reports.

Park *et al*^[15] analyzed the 8 key mutations (G1613A, C1653T, T1753V, A1762T, G1764A, A1846T, G1896A and G1899A) in 442 serum samples of 310 non-HCC and 132 HCC patients to confirm the combinations with HCC. They reported that the BCP combination mutations of ≥ 6 mutations that include G1613A + C1653T + A1846T + G1896A and ≤ 5 mutations with reduced HBeAg production may increase the risk of HCC occurrence compared to only the number of mutations.

In our study, we also found five high frequency mutations ($\geq 10\%$) in the BCP and preC region. We observed thirteen types of multi-mutations in one fragment, among which, 3 types were common combinations ($\geq 5\%$). The three most common multi-mutations were A1762T/G1764A (36%), A1762T/G1764A/G1896A (11%) and T1753 (A/C)/A1762T/G1764A/G1896A (8%). The multi-mutations in HBV genomes (≥ 3) may carry a high risk of liver cirrhosis or HCC. G1896A mutation had an effect on liver disease progression independent of patient age. Additionally, in our study, the results showed that the more viral mutations detected (≥ 3) and G1776A mutation contribute to HBeAg negativity^[16].

Finally, accumulation of mutations, including V1753 and/or A1768 aside from T1762/A1764 in BCP region, were closely associated with HCC among the patients infected with HBV/C1, as shown in a study by Li *et al*^[17]. The BCP mutations have an effect on the biological functions of HBx, increasing the risk of HCC. T1653 mutation in the box- α of the core upstream regulatory sequence and V1753 mutation of BCP region in HBV-infected patients has also been reported to increase the risk of HCC^[17,18]. However, the mechanism between BCP

mutation and hepatocarcinogenesis is mainly unknown.

Several studies have shown that HBV mutations, including C1653T, T1674C/G, T1753V, A1762T/G1764A and C1766T/T1768A in the enhancer II/BCP regions and G1899A, C2002T, A2159G, A2189C and G2203A/T in the precore/core region, are significantly related to an increased risk of HCC^[19].

P REGION GENE MUTATION

One of the regions with mutation susceptibility in HBV ORF is the P region, which encodes the polymerase protein (reverse transcriptase). The envelope (S) gene is completely overlapped by the polymerase gene, so it is logical to assume that changes in virus encoding related to antiviral resistance in the polymerase may have impact on the envelope gene, showing a close relationship between mutations in the S and P regions of the HBV genome^[20]. Mutations in the HBV P gene are frequently associated with drug resistance. Cross-sectional studies on the mutations of this gene are rare. Mutations in this region have not been assumed to be responsible for HCC as frequently as other regions spoken above, but antiviral therapy associated mutations did impact the disease progression on the subject. Several approved antiviral therapeutic agents are available at present, including regular or pegylated interferon and nucleoside/nucleotide analogues (NUCs) such as lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine and tenofovir. The mutation of rtM204V/I with LAM resistance is the most frequent, located at the catalytic YMDD motif. The rtL180M mutation often occurs at the same time. The rtA181T mutation was reported largely in LAM-resistant patients. The rtN236T and rtA181T/V mutations were the most frequent in ADV-resistant patients. ETV resistance is rare in antiviral therapy in naïve patients (1.5% by the fifth year), but if the rtI169T, rtT184A/F/G/I/L/S, rtS202G/I or rtM250V mutation coexists, ETV resistance can occur in the presence of rtM204I/V mutations. The most resistant mutant of telbivudine was rtM204I. Tenofovir has a low risk of drug resistance.

Yeh *et al.*^[21] in a study on 123 LAM-resistant chronic hepatitis B patients reported that the occurrence of the rtA181T/SW172* mutant in LAM-resistant patients could increase the risk of HCC development in the subsequent courses of antiviral therapy.

In our study, we followed up 131 cases of HBV-infected patients who had taken antiviral therapy. The results showed that the antiviral drug resistance was not significantly associated with the progression of the liver disease. Once resistance happened, there was no difference between chronic hepatitis B (CHB) patients with successful and unsuccessful rescue therapy after 6 years. I126T mutation in the S region may be associated with a poor prognosis for patients with CHB. I269L mutation in the P region and I68T mutation in the S region may be associated with poor response of

NUCs treatment. These mutations could be potential new resistant mutations. Whether the mutations mentioned above are related to progression of the liver disease is still to be proved. In our hepatitis B related cirrhosis cohort study, the two year cumulative incidence of HCC in antiviral resistance (DR) patients (30.6%) was significantly higher than that in both complete virologic response patients (4.3%). Of these DR patients especially, the extremely high incidence of HCC was 55.6% in the failed rescue therapy. The rtA181T mutation was closely associated with rescue therapy failure^[22]. It is suggested that the P region gene mutation related DR is associated with chronic hepatitis B development to HCC.

X GENE MUTATION

X ORF produces the HBx and, despite the specific function of HBx, is still undefined during HBV replication. Many studies show that HBx is essential for viral replication *in vivo* and *in vitro*. HBV X gene, extremely easy to mutate and integrate into hepatocytes, plays a significant role in HBV infection and HCC development. Mutations in the X region can effect viral replication through the BCP and the enhancer II. Because the BCP region overlaps with the X gene in the concomitant reading frame, the X gene at xK130M and xV131I was changed by the A1762T plus G1764A core promoter mutations in the aforementioned study^[23].

Wild-type HBx has been proved to activate hypoxia-inducible factor-1 α (HIF-1 α), which could contribute to HCC development and progression. Liu *et al.*^[24] sequenced 101 HCC tissues in Hong Kong. In their study, the double mutations K130M/V131I increased the function of HBx as they upregulated the HIF-1 α expression and transcriptional activity. Wang *et al.*^[25] reported that during the infection and replication of HBV, HBx mutates to adjust itself to the hepatocyte and increase the carcinogenesis. COOH-terminal truncated HBx may play a stimulative part in HBV-related HCC development as well as hydrophobic/hydrophilic character changes in some specific amino acid sites.

Besides, Tuteja *et al.*^[26] reported 222 cases with HBsAg positive patients and they found that T36A and G50R mutations in the X gene were associated with HCC. The integration of the viral genome into the host cellular genome was detected in 80%-90% of these cancers. The viral DNA integration also may cause insertional mutagenesis and result in a 3'-terminal truncation of HBx that was deleted at the C-terminal region by 20-40 amino acids. In the HBx sequence, multiple point mutations may be a consequent change with integration. Moreover, it showed that both truncation and point mutations may increase the oncogenic activation processes. It has been found that the C-truncated HBx proteins transform immortalized liver cell lines and interact with the mutant p53 protein p.R249S to change genetic stability and proliferation of non-transformed hepatocytes in

experimental models^[27]. Lee *et al.*^[19] found that a specific HBx mutation may contribute to the development of HCC in chronic hepatitis B patients by activating nuclear factor-kappa B activity. The HBx 5 mutation in genotype C2 HBV was shown to increase the risk of the development of HCC.

HBV X gene multi-site mutations were found frequently in the clinical HCC tissues. Wang *et al.*^[28] analyzed the HBx gene sequences of 60 cases of HCC tumor tissues and paratumor tissues from China. The results showed that the most frequent mutations were at amino acid 30, 88, 144 from tumor samples and at amino acid 31, 43, 87, 94 from non-tumor samples. It has been found that HBx-linked mutations, such as at aa L30F/S144A, was 29.5% positive in the tumor tissues.

Among the HCC-associated mutations, combined rather than single mutations are associated with the risk of HCC significantly. In the preS region, the frequencies of combined mutations (haplotypic carriage), including 2964C-3116T-preS2 start codon wildtype-7A, 2964C-3116T-7A-76C and 2964A-3116T-7C-76A/T, are significantly higher in patients with HCC than in those without HCC, and yet the haplotypic carriage with single mutation are inversely associated with HCC. In the preS and Enh II/BCP regions, HCC patients have a more frequent occurrence of a haplotypic carriage with 105C and 2962G than those without HCC. The frequency of 2962G-preS2 start codon wild type-105C-1762T/1764A is 47.9% in HCC and 4.3% in those without HCC.

Accordingly, the HBV mutations, either in the preS or in the core promoter region, are significantly associated with HCC, whereas the wild-type nucleotides in these regions are mostly associated with liver cirrhosis. HBV mutations can be used as indicators for the prediction of end-stage liver diseases, including HCC. Although these mutations and the combinations are specific for HCC to some extent, it will be more practical if they can predict the malignancy in HBV-infected subjects before the occurrence of HCC.

IN THE FUTURE

Many factors have an effect on the development of HBV-associated HCC, including products of HBV, HBV integration and mutation and host susceptibility. HBV sequences from these individuals demonstrate numerous mutations/deletions and alterations that can result in decreased immune recognition of the virus, thereby affecting the expression and functions of specific genes and contributing to liver disorders. However, the aforementioned studies mostly lacked a series of observation and detection. Additionally, sequencing the HBV genome to find the HCC-related HBV mutations have conflicting results, suggesting that the pathogenesis of development to HCC is a combination. The hepatocarcinogenesis of chronic inflammation, host immunity and environment in chronic hepatitis B

patients with different patterns of mutation should be further studied.

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