

Review Article

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## Pathogenesis of Hepatitis B Virus

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### ABSTRACT

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Hepatitis B virus (HBV) is one of the most prevalent pathogens in the world and infection with this virus is a serious threat for public health. The pathogenesis of HBV depends on the critical interplay between viral and host factors. The review briefly highlights genotypes & mutations with association of disease progression and immune response during infection.

### Introduction

Hepatitis B virus (HBV) is a global public health problem (Oakes, 2014). It is reported that 2 billion people have exposed and 350 million people chronically infected with HBV (Oakes, 2014, Tillmann *et al.*, 2012). The chronic infection further lead to cirrhosis and hepatocellular carcinoma (HCC), resulting into one million deaths worldwide annually (Oakes, 2014).

In human, HBV infection can be influenced by some of major factors such as existence of various genotypes, mutant species and immune status of the host (Pan *et al.*, 2005). The establishment of liver disease is largely driven by complex interaction between the virus and host. Therefore the present review provides recent information on genotypes and mutations of HBV with association of

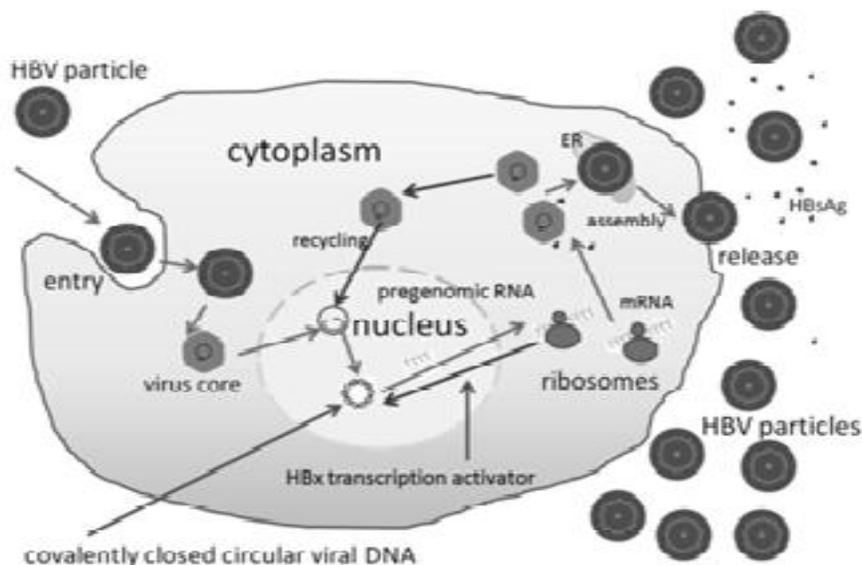
disease progression and immune response during infection in human.

### Background

HBV, an enveloped DNA virus of Hepadnaviridae family, has genome size of 3.2kb (Locarnini and Zoulim, 2010). The major route of transmission of HBV is perinatally from hepatitis positive chronically infected mothers or via early horizontal transmission from close contact with immediate family members or sexual contact. HBV is survival for 6 months at room temperature and 7 days at 44°C.

The HBV virion first attaches to a hepatocyte, penetrates the cytoplasm of hepatocytes (Locarnini and Zoulim, 2010) (Fig.1), moves into the hepatocytes nucleus

**Fig.1** Life Cycle of Hepatitis B Virus



**Table.1** Major stages of chronic hepatitis B infection

<b>Immune tolerance Phase</b>	This phase commonly occurs in infants who are infected via perinatal transmission from Hepatitis B surface/envelop positive mother. During this phase, there appears to be either no or minimal liver inflammation or fibrosis.
<b>Immune clearance phase (immunoactive)</b>	Active liver inflammation with or without liver fibrosis. There is minimal liver damage and transition from immune tolerant to clearance phase occurs in the earlier life (late childhood adolescence or adulthood).
<b>Inactive carrier phase (immune control)</b>	In this phase no further damage to the liver occurs. This phase may convert into immune clearance phase, reactivation phase or immune control phase.
<b>Reactivation phase</b>	Reactivation phase can be spontaneous or can be triggered by Immunesuppression

and convert the DNA to covalently closed circular DNA (cccDNA) – a double stranded DNA structure (Oakes, 2014). The DNA is very stable and can stay in the host nucleus for many months in chronic diseases. The newly formed HBV particles are released into the bloodstream, invade other hepatocytes and repeat the replication process.

In adult, approximately 90% of infection are acute and only 5-10 % develop into chronic infection. There are four stages of chronic infection i.e., immune tolerance phase, immune clearance phase (immunoactive),

inactive carrier phase (immune control) and reactivation phase (Kim *et al.*, 2011) (Table 1) but not all chronic infected patients go through all the four stage (Shi, 2012). The rate of progression from acute to chronic infection is approximately 90% of infections acquired in the perinatal period whereas 30-50 % for infections between the ages of 1 and 5 years and < 5 % for infections acquired in adulthood (Kim *et al.*, 2011). The risk of developing cirrhosis with chronic infection is 15-40 % during life time with a 2-5 % risk of hepatocellular carcinoma with cirrhosis.

**Table.2** Hepatitis B Virus genotype and disease outcome.

<b>Genotype</b>	<b>Geographic distribution</b>	<b>Disease outcome</b>
Genotype A	Sub-Saharan Africa, India, Brazil, Argentina, Europe, United States, Arctic, Australia and West Africa	Hepatocellular carcinoma develops in young males often without cirrhosis. Hepatocellular carcinoma and cirrhosis develop in older person
Genotype B	Japan, East Asia, Northern Canada, Greenland	Hepatocellular carcinoma and cirrhosis develop in older person.
Genotype C	China, Korea, Southeast Asia, Japan, South Pacific Islands, Australia	Risks for Hepatocellular carcinoma and cirrhosis are higher than genotype B
Genotype D	Russia, Middle East, Mediterranean Mongolia, North Africa, Europe, Indian Subcontinent, Arctic, North and South America, Australia	Hepatocellular carcinoma and cirrhosis develop in older individuals
Genotype E	West and Central Africa	Little is known about the clinical outcomes related to this genotype
Genotype F	Alaska, Central America, South America, Bolivia, Argentina	Associated with Hepatocellular carcinoma which developed in children and young adults in Alaska only
Genotype G	Europe, United States	Almost exclusively found in persons coinfecting with other genotype mainly A.
Genotype H	Central America	Not studied
Genotype I	Vietnam and Laos	Not studied
Genotype H	Japan	Not studied

The mechanism by which chronic infection predisposes to the development of HCC is not clear. Hepatocyte inflammation, necrosis, mitosis are major factors in nodular regeneration, fibrosis and carcinoma.

### **HBV Genotypes and HBV Mutations with Association of Diseases Progression**

#### **Genotypes**

Genotype of Hepatitis B virus appears to play an important role in host viral interactions influencing clinical symptoms progress (Tanwar and Dusheinko 2012). There are 10 geographically distributed HBV genotypes (Table 2). These genotypes have a divergence of the viral DNA of about 8%. HBV subgroups have been identified within different HBV genotypes when an

intra-genotype difference of >4% and <8% was applied to the complete nucleotide sequence (Kao, 2011).

HBV is endemic infection in Asia and Pacific islands, south Europe and Latin America. Genotype A is highly prevalent in sub Saharan Africa (Subtype A1), Northern Europe (Subtype A2 and Western Africa (Subtype A3). Genotype B has six subtypes B1-B6. Genotype B1 is found in Japan, Genotype B2-B5 in East Asia and B6 in Arctic regions including Alaska, Northern Canada and Greenland. Genotype C which has subtypes C1-C5 is found primarily in East and Southeast Asia. Genotype D has subtypes D1-D5 which is prevalent in Africa, Europe and India. Genotype F which has 4 subtypes (F1-F4) is found in Central and South America (Kao, 2011). HBV genotypes E, G and H are uncommon and

their effects on disease outcome are not well characterized (Kim *et al.*, 2011).

The rates of disease progression and incidence of advanced liver diseases may vary from each HBV genotype and are influenced by environmental host and viral factors. HBV genotypes A, B, C, D and F are known to cause hepatocellular carcinoma (Tong *et al.*, 2013). In Europe and Asia, most patients with genotype A and B have acute hepatitis B infection (Shi, 2012). Infection by Genotype C or D is significantly more likely to lead to cirrhosis and hepatocellular carcinoma than genotype A or B (Kao, 2011). The pathogenic differences among various HBV genotypes have been partially clarified. Intracellular

expression levels of HBV DNA, HBV core antigen as well as HBV envelop antigen have been found to be higher for HBV-B and C genotypes than for HBV-A and D. The intracellular accumulation of HBV DNA and viral antigens may play a role in inducing liver cells damage (Kao, 2011). HBV genotype F1 has shown to be associated with high risk of HCC as compared with HBV genotype A, B and D particularly in children and young adult (Kim *et al.*, 2011, McMahon, 2009). Accumulating evidence suggests that a patient with chronic HBV infection should receive HBV genotyping unless he or she lives in a country known to harbor only HBV genotype.

**Table.3** Important HBV mutants and its clinical impact

Genomic region	Molecular effect	Clinical relevance
Pre-S/S	Pre-S1/pre-S2 mutations, S gene Mutations	Fibrosing cholestatic hepatitis high risk for HCC
Pre-C/C	Pre-C stop codon mutations, Core promoter mutations	Viral persistence,, severe forms of disease, high risk for HCC
Pol	Pol gene mutations	Viral persistence
Regulatory sequences	Core promoter mutations	Severe hepatitis
X gene	Truncated X gene	high risk for HCC

**HBV Mutants**

The virus uses reverse transcription to copy its DNA genome during HBV replication. However, this HBV polymerase lacks proof reading ability, allowing mutations to occur which leads to a heterogeneous population of HBV (Horvat, 2011). HBV genome seen to play a vital role in different outcome of this infection (Table 3) (Baumert *et al.*, 2007). Mutations in HBV surface (S), precore (PC) and basal core promoter (BCP) genes are observed frequently in HBV infected patients and these mutations are

associated with the clinical outcomes of HBV disease (Laiang *et al.*, 2013).

The pre-S domain is the essential binding site for hepatocyte receptors and preS1 and PreS2 region is the most variable region in the HBV genome. Mutations at Pre-S region is observed in chronic, fulminant and acute hepatitis (Shen and Yan, 2006, Utama *et al.*, 2012, Heo *et al.*, 2013). A novel preS1 mutation W4P/R is observed significantly related to severe liver diseases male predominance from Korea (Lee *et al.*, 2013).

Mutations T207A and T770C in the small S region were observed in cirrhosis and Hepatocellular carcinoma (Veazjalali *et al.*, 2009). The basic core protein and its adjacent precore region are crucial for replication of HBV. Mounting evidence has emerged to demonstrate that BCP and preC mutants are predisposed to severe and progressive liver diseases after HBV infection, causing an increased risk for hepatocellular carcinoma. Mutations in the C region were found to be significant related to hepatocellular carcinoma (Liang *et al.*, 2013, Yuen *et al.*, 2008). Six types (preC-W28, C-P5H/L/T, C-E83D, C-197F/L, C-L100I and C-Q182K/) and seven types (PreC-W28, PreC -G29D, CD32N/H, C-E43K, C-P50A/H/Y, C-A131G/N/P and C-S181H/P) mutations in the preC/C region is found to be related to hepatocellular carcinoma (Kim, 2012). G1613A and C1653T double mutations are frequently found in patients with HCC. A single G1613A mutation is associated with future emergence of HCC (Tatsukawa, 2011). Hepatitis B virus X gene is the smallest kinds of HBV functional genes and currently available evidence supports a role in pathogenesis of HBV induced hepatocellular carcinoma (Kew *et al.*, 2011). Accumulation of eight key mutations located in the X/preC regions of the HBV genome (G1613A, C1653T, T1753V, A1762T, G1764A, A1846A and G1899A) is a risk marker for the development of HCC (Park *et al.*, 2014).

These above mentioned clinical studies shows that strong association between HBV mutations and hepatocellular carcinoma,

### **Immune Response during Acute and Chronic infection**

Infection with HBV can be either acute or chronic. Adult infections have a relatively low rate of chronicity (around 5%) and

neonatal infections usually have a high persistence rate (Busca A. Kumar, 2014). HBV carriers are at risk of developing life threatening cirrhosis and later on hepatic carcinoma.

Within hours after HBV infection, there is a transient release of IL- 6. IL-6 ensures early control of the virus and preventing death of the HBV infected hepatocytes. HBV replication tends to be enhanced 3-4 days after infection when IL-6 level has returned to baseline.

During the early phases of acute viral infection, natural killer (NK) cells are activated and reduce the viral load through the secretion cytokines (Ishikawab, 2012). In the liver NKT cells are higher than in other organs. This activation of natural killer cells is rapidly suppressed by interleukin IL-10 indication that the roles of NK cells on HBV regulation are limited (Dunn *et al.*, 2009; Ishikawa, 2012).

During the immune active phases of chronic infection, the cytotoxic T lymphocytes (CTL) response begins to destroy HBV infected hepatocytes leading to reduced viral load and liver damages. Because the CTL response associated with chronic HBV infection is weak and inefficient, the cycle of hepatocyte destruction and reinfection by HBV continues for decades.

HBV replication is not directly cytotoxic to cells. The treatment of patients is to prevent the development of cirrhosis and hepatocellular carcinoma (Busca and Kumar, 2014). Antibodies against HBsAG, HBeAG and CoreAG are produced and prevent viral spreading from one to another hepatocyte and also block circulating HBV.

The pathogenesis and clinical manifestations of HB infection are due to interaction of

virus and the host immune system. The known major risk factors for HBV related HCC can be categorized into virus factors, host factors and host virus interactions. Long term suppression of HBV is associated with substantial histological improvement and reversal of fibrosis or cirrhosis. Cirrhosis is a cardinal factor in carcinogenesis. Hepatocyte inflammation, necrosis, mitosis and feature of chronic hepatitis are major factors in nodular regeneration and fibrosis. A key mechanism for hepatocarcinogenesis is the integration of HBV DNA into the host genome and the formation of covalently closed circular DNA (cccDNA). HBx has an important role in activating HBV transcription and replication and in the development of HCC. The mechanism by which chronic hepatitis B infection predisposes to the development of HCC is not clear. Patients with chronic hepatitis B are at significant risk for hepatocellular carcinoma.

### **Future Research**

During the past decade, some important information on pathogenesis of HBV was generated but still few questions remain to be unanswered.

The HBV virion moves into the hepatocytes nucleus and convert the DNA to covalently closed circular DNA (cccDNA) – a double stranded DNA structure. How is cccDNA converted from Relaxed Circular (RC) DNA? Does this process involve host cellular DNA repair enzymes? If yes, than further studies are required to elucidate it.

Many studies have shown that HBV genotypes have remarkable clinical and epidemiological differences, However, HBV subgenotypes, mixed genotype infection and the effect of different genotypes on the treatment of HBV infections require further studies.

Considerably, many cellular (microRNAs) indirectly influence the HBV life cycle by regulating the expression of relevant cellular proteins and may play important roles in hepatitis pathogenesis. Future studies need to be performed to elucidate the regulatory loop involving miRNAs and the cccDNA epigenetic machinery and certainly to investigate how to translate these finding into clinical applications.

In conclusion, from all these information, it is observed that pathogenesis is a very complex involving multiple aspects. Though, important aspects have been highlighted here, still there is potential for new discoveries that will facilitate for better understanding of the HBV pathogenesis. New discoveries which are of direct benefit for the affected patients will eventually help to improve the management of the disease.

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