HEPATITIS B VIRUS; STRUCTURE, REPLICATION MECHANISM, AND VARIANTS

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SUMMARY

The human hepatitis B virus (HBV) elicits acute and chronic liver disease in humans and has been linked to hepatocellular carcinoma. The virus is transmitted by perinatal exposure, sexual contact, exposure to blood products and organ/tissue transplantation. HBV is a member of the hepadnavirous family and the viral genome within the HBV particle is a circular, partially double-stranded, relaxed-circular DNA molecule. The infectious particles are called Dane particles and consist of an icosahedral nucleocapsid surrounded by a lipoprotein envelope. The promoter, enhancer, poly-A addition signal and glucocorticoid-responsive element (GRE) are signal sexuences which are involved in HBV gene expression. The virus replicates via an RNA pre-genome using covalently closed, circular, double stranded DNA as a transcriptional template. Multiple mutant variants have been identified and characterized at the molecular level with certain clinical syndromes.

Key Words : Hepatitis B virus, HBV replication, HBV variants

INTRODUCTION

Hepatitis B virus (HBV) infection is known as the most important chronic virus infections in the world. HBV causes a spectrum of clinical manifestations, ranging from mild, inapparent infection to fulminant hepatitis, severe chronic liver disease and cirrhosis (1). The virus also has been clearly implicated in the development of primary hepatocellular carcinoma (HCC), one of the most common cancers in the world (2). HBV is a member of the hepadnavirus family, characterized by a small genome of circular, double-stranded DNA which replicates by reverse transcription (3-6). Sequence analysis of HBV genomes obtained in the sera of infected individuals with unusual serologic profiles indicated clinically important HBV variants having mutations within pre-core (pre-C), pre-S and S regions (7). Definition of the variations in HBV gene expression and host response is essential in elucidating the biologic mechanisms underlying atypical HBV infection and consequent disease. Although genomic structure, function and the replication cycle of HBV are wellknown, determination of the significance of extrahepatic infection, and establishing the importance of HBV variants in the clinical area which relate to the pathogenesis of HBV-induced disease remain to be determined.

This paper will provide a brief overview of the molecular biology of HBV.

EPIDEMIOLOGY OF HBV INFECTION

HBV currently is the most important chronic virus infection in the world. At present, more than 300 million people worldwide and 1.5 million people in the United States are chronic carriers of this virus, and a significant number of these individuals will die from either liver failure or hepatocellular carcinoma (HCC) (7). Asia is a hyperendemic area for hepatitis B. In some countries more than 70% of the population over the age of 40 years shows signs of previous infection (8). In Africa, prevalance of the disease is almost universally high, with a chronic carrier rate of around 10%. In the Mediterranean countries and eastern Europe, the prevalance among blood donors are found to be slightly higher than 0.1% (8). In Turkey, prevalance among blood donors is detected as 4.5% (9).

The virus is transmitted parenterally, perinatally, and by sexual, intimate, or close personal contact (10). Intravenous (IV) drug abusers, multipartner heterosexual men and women and homosexual men, sexual partners of HBV carriers, infants born to HBV-infected mothers, patients and staff in custodial institions for the developmentally disabled, recipients of certain plasma-derived products, hemodialysis patients, health and public-safety workers who have contact with blood, and persons born in areas of high HBV endemicity are the persons at increased risk of infection (11). Parenteral transmission may occur from the use of unsterile medical and dental instruments, hemodialysis, ear piercing, prophylactic inoculations, and acupuncture.

MOLECULAR BIOLOGY AND REPLICATION MECHANISMS OF HBV

HBV is a member of the hepadnavirus family (hepatotropic DNA virus) (3-5). Closely related viruses have been characterized including woodchuck hepatitis virus (WHV) found in Eastern woodchucks, ground squirrel hepatitis virus (GSHV) isolated from Beechey ground squirrels, duck hepatitis B virus (DHBV) isolated from Pecking ducks (9). Others have been detected in domestic geese, herons, snakes, kangaroos, and the tree squirrels (12, 13). All have similar virion structure, genome organization, and mechanism of viral replication (14).

The infectious particles are called Dane particles (48 nm) and consist of an icosahedral nucleocapsid surrounded by a lipoprotein envelope. The HBV envelope is composed of three polypeptides of different sizes: major, middle and large envelope proteins. Nucleocapsid which is 28-nm in diameter and composed of the core protein contains the viral genome and viral encoded DNA polymerase. The viral genome within the HBV particle is a circular, partially double-stranded, relaxed-circular DNA molecule. The complete strand is approximately 3200 base pairs (bp) in length (Fig. 1) (3-7). It is asymmetrical and consists of a long circular strand, L(-), associated with a short strand of a variable length, S(+). These asymmetries are important in the strategy for genome replication. The transcript of the long (L), or minus strand of the genome contains four major open reading frames (ORFs) encoding structural proteins (nucleocapsid and envelope) and nonstructural proteins (DNA polymerase and transcriptional transactivator); pre-S/S, which encodes the surface antigen proteins of the virion envelope; pre-C/C, which encodes the core antigen of the nucleocapsid; P, which encodes the DNA polymerase activities of the virus; and X, which encodes the X protein. The exact function of the X gene is still unknown (15) but HBx can be detected in the liver of many HBV-infected individuals (16, 17). HBx may enhance HBV replication (18) through activating transcription, and it may also be involved in hepatocarcinogenesis (19).

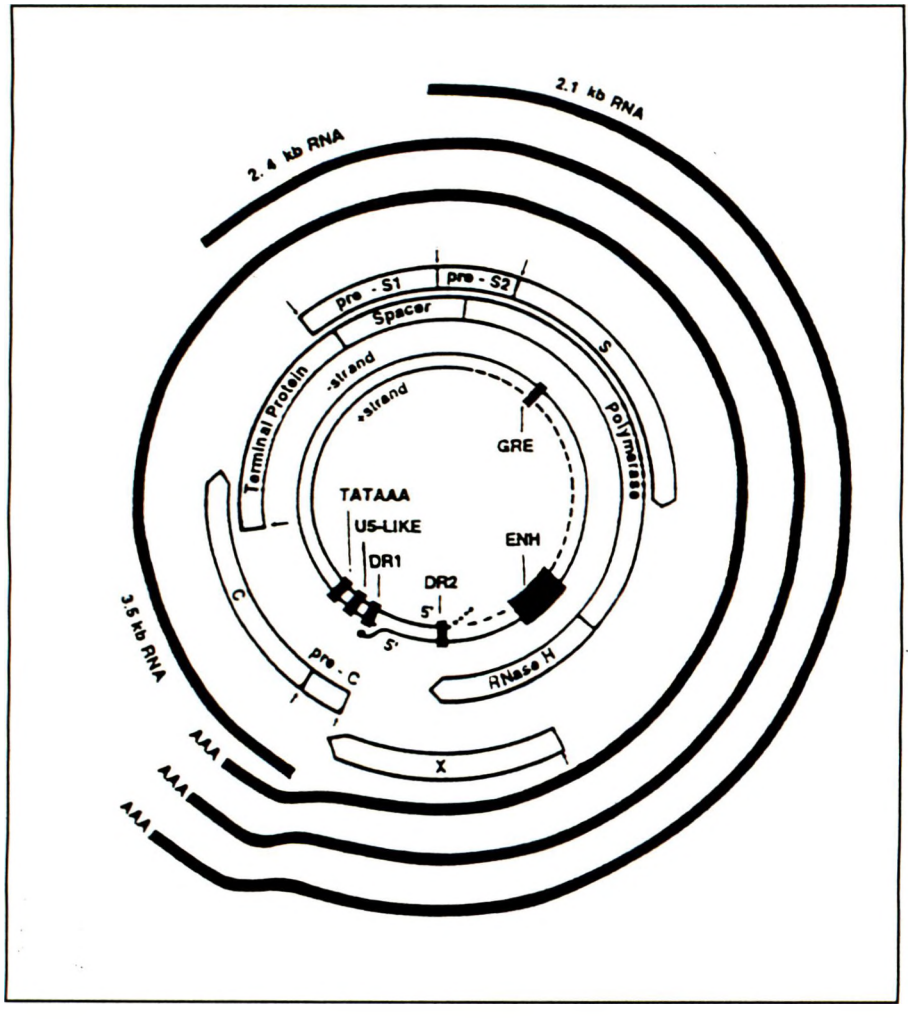

Fig. 1: Structure, genome organization, and transcripts of the HBV genome.

There are four types of signal sequences that appear to be involved in HBV gene expression, namely: (1) the promoter; (2) the enhancer; (3) the poly-A addition signal; and (4) the glucocorticoid-responsive element (GRE).

A promoter is a nucleotide sequence that acts as a binding site for RNA polymerase, a host cell-derived enzyme that synthesizes RNA from a DNA template. Most eukaryotic cell and virus proteins are expressed from poly-A^+ mRNA transcripts synthesized by RNA polymerase II. There are at least four distinct, functionally-defined RNA polymerase II promoters located near the 5'-end of each of the virus transcripts since there are four HBV-specific, unspliced RNA transcripts. The promoter for 3.5-kb mRNA transcript is located within the X gene sequence and contains highly abundant RNAs that are slightly longer than genome length and contain a short terminal redundancy. These RNAs can be divided into two subsets on the basis of size and function. In one, the RNA initiates before the pre-C initiation codon and serves as the message for the pre-C/C protein, the secreted HBeAg polypeptide. In the other, initiation occurs after the pre-C initiation codon and the resulting RNA is a bifunctional molecule serving as the template for reverse transcription as well as the transcript for the synthesis of the core and polymerase polypeptides. The 2.1-kb subgenomic transcripts encode the S and M envelope proteins, whereas the 2.4-kb and 0.9 -kb classes of RNA are thought to encode the L envelope and X proteins, respectively (20). On the other hand, two spliced transcripts have been detected in HBV-infect tissues and transfected cells (21-23). Genetic analysis has revealed that neither is required for HBV replication *in vitro* (24), however, each of these transcripts has a biological role *in vivo* (25).

Two transcriptional enhancers, enhancer I and enhancer II, are located immediately upstream of the X ORF within the P coding region and upstream of the C promoter, respectively (26, 27). The DR1 and DR2 elements (11-bp) which are direct-repeat sequences locating at either side of the cohesive ends of the genome play an important role in viral DNA synthesis (28).

Poly-A addition signal sequences are essential for the termination of transcription and the addition of poly-A 'tails' to the 3'-end of mRNA molecules. Each of HBV-specific, unspliced RNAs terminate at a common position just downstream of a variant polyadenylation signal (TATAA) located in the core antigen coding region (29).

A glucocorticoid-responsive element (GRE) is a segment of DNA that binds a hormone receptor which, in turn, acts to increase the level of transcription of a given gene. This element contains an 18-bp sequence that is homologous to other known GRE. The role of this element in the expression of HBV genes in virus infections awaits further work. However, one group has shown that the surface antigen gene expression in transgenic mice is regulated by sex steroids and glucocorticoids (30). Thus, control of gene expression by the HBV GRE may account for the observed differences in the biology of HBV infections between the sexes.

Although classified as double-stranded DNA viruses, the hepadnaviruses replicate via an RNA pregenome using covalently closed, circular, double-stranded DNA (CCC/DNA) as a transcriptional template (31). During the hepatitis B replication in hepatocyte, virus penetrates the hepatocyte membrane which recognizes a peptide encoded by pre-S1 and uncoats. After reaching the hepatocyte nucleus, the partially double-stranded HBV-DNA is converted by DNA polymerase into a fully double-stranded circle within the hepatocyte nucleus. L(-) strand is transcribed to a 3.5 -kb RNA (pregenome) by host cellular RNA polymerase. The pre-genome is transported out of the nucleus to the cytoplasm where the core protein is made and encapsulates the pre-genome RNA plus the newly synthesized DNA polymerase and DNA-linked protein. The viral (-) strand is then synthesized from the pre-genome RNA template, presumably using the viral DNA polymerase as a reverse transcriptase. As HBV-DNA is synthesized, the pregenome RNA is degraded except for a small fragment probably used to prime the synthesis of the (+) strand from newly-synthesized L(-) template. Finally, the progeny particles gain HBsAg-containing envelopes, probably by budding from the cell's plasma membrane and become infectious virions.

HBV VARIANTS

In recent years, it has become apparent that genotypic variations in the HBV genome may result in an HBV infection capable of inducing significant and transmissible disease with atypical serologic patterns. With the recent advances in molecular biology techniques, multiple mutant variants have been identified and characterized at the molecular level with certain clinical syndromes (32-36).

The pre-C/C gene can be translated into either core protein (HBcAg), or HBeAg, a protein found in serum and probably on the hepatocyte surface. The gene that encodes both proteins has two initiation codons for protein synthesis. The first (or pre-C) start codon leads to synthesis of HBeAg, while use of the second (or C) start codon generates HBcAg. Thus, the coding region between these codons (the pre-C region) is unique to HBeAg and encodes a signal sequence for protein transport into the secretory parthway; once in this pathway, the protein undergoes proteolytic cleavage at its C terminus to generate the mature 16 kD HBeAg, which is then secreted into the serum. HBcAg, lacking this targeting signal to the secretory pathway, accumulates in the cytoplasm (and nucleus) and is used for construction of progeny Dane particles. HBeAg correlates with infectivity because its mRNA is co-regulated with that

of HBcAg, and the latter RNA is essential for Dane particle synthesis. Chronic carriers of HBV eventually lose HBeAg and seroconvert to anti-HBe. After an exacerbation of hepatitis, while the liver disease becomes quiescent, some patients having progressive disease with high concentration of HBV DNA in serum are detected. During the seroconversion to anti-HBe, mutant viruses are selected that can no longer express HBeAg (33, 37, 38) because of a translational defect in the pre-C region of the C gene. The most clinically important mutation causing this defect is a glycine to arginine variation at nucleotide 1896 within the pre-C region, which changes the 28th codon from TGG to TAG, a stop codon prematurely terminating translation of HBeAg before the end of pre-core. However, even in the absence of HBeAg, this variant which is known as Mediterranean variant, is associated with active liver disease, elevated alanine aminotransferase (ALT) levels, hepatic HBcAg, and relatively high levels of serum-and liver-associated HBV DNA. Interferon treatment appears to be less effective and HCC development and mortality appears to be significantly higher in patients with such pre-C mutations than with wild-type HBV (36). In adition, several studies have now demonstrated a strong association between fulminant hepatitis B and the recovery of HBeAg-negative variants (3, 27, 35,39).

The second and probably most common variant of HBV contains mutations in the pre-S and S genes. The surface of the Dane particle contains 3 related glycoproteins, all translated from a single coding region by initiation of different start codons. Initiation at the most internal start codon generates the 24 kD S protein, the classical HBsAg. Initiation at the upstream (pre-S) start sites yields two larger proteins, preS2 (31 kD) and preS1 (39 kD); these thus contain all the sequences of S, plus added extensions at their N-termini. The major protective epitope of HBV is highly conserved and found within 23 amino acids of the surface antigen (HBsAg). HBV vaccination does not produce protective immunity againts infection with mutants of this epitope (40). Most cases had a mutation from glycine to arginine at amino acid 145 of HBsAg within this region which is first detected in infant born to a carrier mother who developed HBV infection despite HBV vaccine administration. Importantly, the mother's virus contained only the normal glycine at this position, which maps to the major immunodominant epitope of HBsAg. Other mutations do not seem to be as important in this region. Although the virus with arginine at amino acid 145 is infectious, there are no data on how far such a virus has spead within the vaccinated population or the population at large(41). Although there is little information on the prevalence of such mutations in other areas of the world, obviously such studies are important to change the vaccine.

Because HBV infection is diagnosed with serological tests of antigen/antibody reactions, changes in HBV antigenic structure may affect the sensitivity of these tests. Assessments of the importance of such mutants should use polyclonal-based assays, as current monoclonal assays will not detect the mutant. An increasing accessibility to the tools of molecular biology will lead to rapid progress in this area and perhaps to the identification of additional biologically significant HBV variants.

EXTRAHEPATIC INFECTION

Since the predominant feature of hepadnavirus infections is liver injury, it had long been assumed that these viruses were strictly hepatotropic and that the observed extrahepatic manifestations were mediated by circulating immune complexes. However, more recent evidence indicates that hepadnaviruses also can associate with cells of extrahepatic origin.

Until recently, studies to analyze extrahepatic infection in man, had utilized readily accessible white blood cells obtained from patients with HBV infection. Molecules resembling liver-associated, replicative intermediates of the viral genome have been found in monocytes (42). *In vitro* studies showed that human bone marrow cells were susceptible to HBV infection and suggested that the virus exerts an inhibitory effect on myeloid differentiation (43).

At the present time, only limited information is avaible regarding HBV sequences and gene products in nonlymphoid, extrahepatic tissues. Preliminary studies demostrated the presence of HBV sequences in bile duct epithelial and liver endothelial cells and also viral DNA detected in multiple organs including pancreas, kidney, and skin. In recent studies of two patients with fulminant and resolving hepatitis, fast-migrating, low-molecular-weight forms resembling replicative intermediates were detected in DNAs extracted from lymph nodes, spleen, gonads, thyroid, kidney, pancreas, and adrenals with the most intense signal of hybridization in lymph node DNA (44) .

Remarkably, little or no HBV-related DNA sequences were found in serum or liver. In contrast studies to evaluate patients with chronic HBV infection, revealed that the majority of HBV DNA was present in the liver.

HBV DNA INTEGRATION IN HEPATOCELLULAR CARCİNOMA

Chronic HBV infection is epidemiologically correlated with hepatocellular carcinoma, and neoplastic cells often contain mono-or oligoclonal HBV genome fragments integrated into their chromosomes. HBV may be considered as a human tumor-inducing virus from a theoretical, biological and clinical point of view. HBV can induce liver tumor formation by at least two distinct mechanisms. Integration of HBV into host chromosomal DNA may cause the activation cellular oncogenes either directly or by disruption of tumor suppressor gene function (45-47). Continuous

process of cell death and regeneration which are resulted by chronic inflammation, may increase the probability of the occurrence of a critical mutational event and subsequent tumor formation (48). Since tumorigenesis is a complex, multistep process, both mechanisms might, in some cases, cooperate in the development of HBV-related HCC.

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