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An Overview of Hepatitis B Virus Structure Pathology and Therapeutics

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Abstract: ***The hepatitis B virus is a DNA virus belonging to the* Hepadnaviridae *family causing hepatitis B in humans. Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease. Treatment of Hepatitis B***

- ***The goal of treatment for chronic hepatitis B is to suppress HBV replication, prevent the progression of liver disease and thereby the development of cirrhosis, liver failure and HCC.***
- ***Interferon alpha (α-IFN) is the first-line treatment option for patients without cirrhosis. Interferon has antiviral, anti-proliferative and immuno-modulatory effects.***
- ***At a dose of 100 mg daily, lamivudine leads to a marked reduction or elimination of detectable HBV DNA in plasma in about 40% of HBeAg positive and 60–70% of HBeAg negative patients.***
- ***Telbuvidine is a L-nucleoside analogue with potent anti-HBV activity. It is similar to lamivudine in mechanism of action and resistance profile but is more potent. However, its use is limited due to a high rate of resistance and cross-resistance with lamivudine.***
- ***Emtricitabine is another L-nucleoside analogue with similar activity to that of lamivudine.***
- ***Adefovir is a nucleotide analogue of deoxyadenosine monophosphate that has demonstrated efficacy in suppressing HBV DNA (20–50%) and normalizing liver function (50–70%).***
- ***Entecavir is a carbocyclic analogue of 2′ deoxyguanosine. It is a potent suppressor of HBV replication, resulting in loss of serum HBV DNA in 70–90%, and ALT normalization in 70–80% of patients.***
- ***Tenofovir is a nucleotide analogue initially approved for the treatment of HIV. It is often used in a coformulation with emtricitabine. After 48 weeks of therapy with tenofovir, HBV DNA loss is achieved in 80–90% and ALT normalization in 70–80% of patients.***
- ***Orthotopic liver transplantation is a treatment for chronic hepatitis B end-stage liver damage. However, the risk of reinfection on the graft is at least 80% with HBV presumably from extrahepatic reservoirs in the body.***

Keywords: Hepatitis B, virus structure, mechanism, disease, DNA, virus cure

1. Introduction

Hepatitis B virus (HBV) is a hepatotropic virus that can establish a persistent and chronic infection in humans through immune anergy (Figure1A). Currently, 3.5% of the global population is chronically infected with HBV, although the incidence ofHBV infections is decreasing owing to vaccination and, to alesser extent, the use of antiviral therapy to reduce the viral load of chronically infected individuals. The course of chronic HBV infection typically comprises different clinical phases, each of which potentially lasts for decades. Well-defined and verified serum and liver biopsy diagnostic markers enable the assessment of disease severity, viral replication status, patient-risk stratification and treatment decisions. Current therapy includes antiviral agents that directly act on viral replication and immune modulators, such as interfere on therapy. This project addresses several aspects of HBV

***Fact*:** In 1967, Krugman and colleagues 188 identified two types of hepatitis, which were termed MS-1 and MS-2. MS-1 was typically acquired through the oral route after a short incubation period, whereas MS-2 was ostensibly transmitted parenterally with a long incubation period. MS-1 and MS-2 hepatitis were subsequently classified as hepatitis A and B, respectively infection, including epidemiology, immune pathophysiology with a brief outlook on diagnosis, prevention and management.

HBV has an easily available vaccine but no cure. Approximately 257 million individuals are infected with HBV globally, and nearly 900,000 die each year related to disease complications, including liver failure or hepatic cancer. Chronic HBV infection is a major publichealth problem. According to the WHO, mortality due to viral hepatitis is increasing. In 2000, 1.1million individuals died of viral hepatitis globally; this number increased by 22% to 1.3 million individuals in 2015. In 2015, approximately 0.8 million deaths were attributed to HBV infection (Figure1B).

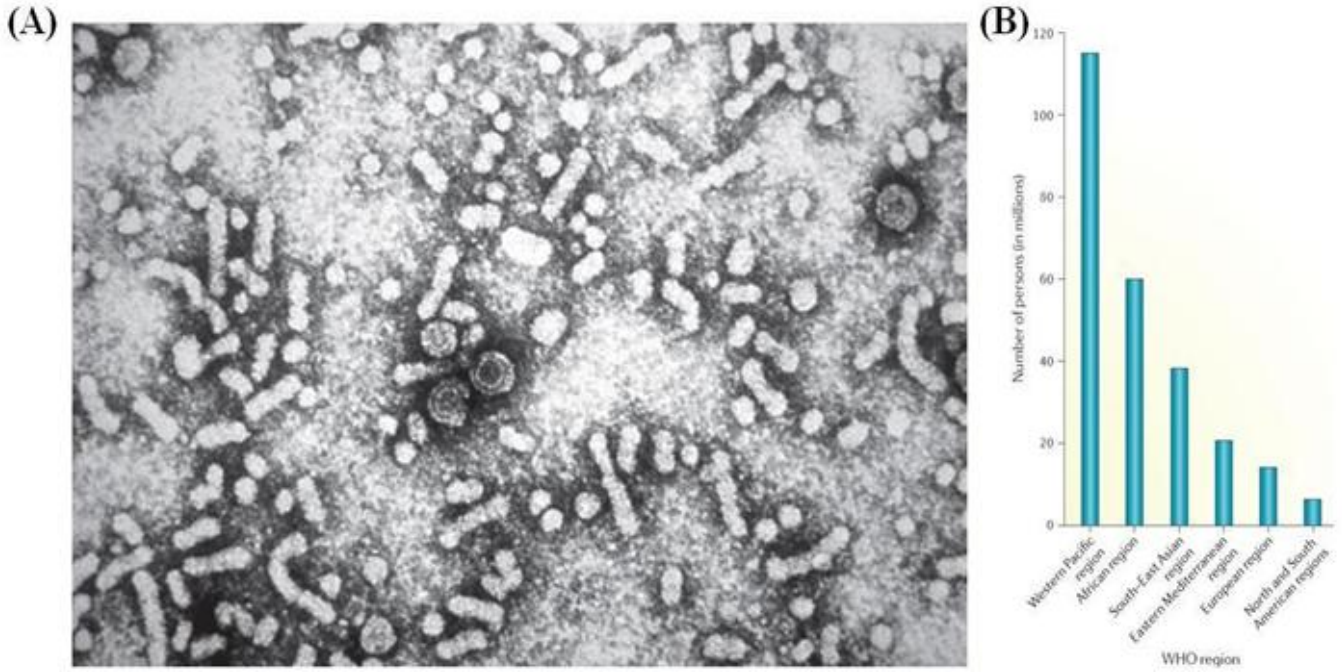

Figure 1: (A) Hepatitis B virions and subviral particles under electron microscopy. Electro micrograph of hepatitis Bvirus (HBV) showing complete double-shelled virions (Dane particles) and excess sub viral particles (containing hepatitis B surface antigen) in tubular and small spherical form. (B) Population size of chronic hepatitis B carriers in different WHO regions.

Structure

The infectious HBV virion (Dane particle) has a spherical, double-shelled structure 42 nm in diameter, consisting of a lipid envelope containing HBsAg that surrounds an inner nucleo capsid composed of hepatitis B coreantigen (HBcAg) complexes with virally encoded polymerase and the viral DNA genome. The envelope surrounds an icosahedral nucleo capsid, (Figure2) which encloses a partially double-stranded, relaxed circular DNA (rcDNA) genome of ~3.2 kilobases. Four partially overlapping open reading frames (ORFs), termed P (polymerase), S (surface), C (core) and X (HBx protein) define the coding capacity of the HBV genome. The hepatitis B virus is interesting in its ability to use relatively few virusproteins to carry out a wide range of actions. HBcAg exists as a soluble dimer with an RNA binding domain. The structure of HBcAg dimers can vary with dimers in capsids being more compact than free dimers in solution.

Regulation of HBcAg can change the conformational state of the dimers which affects their functional state. An example is the oxidization of core protein dimers which leads to weaker dimer-dimer interactions, slowing down capsid assembly. The ability for HBcAg to switch between different structural states is crucial for its function in capsid assembly and HBV virology.

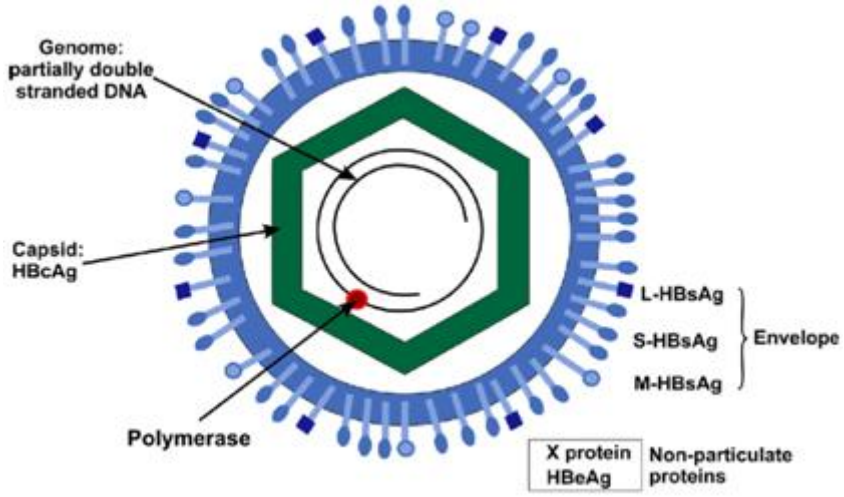

Figure 2: Structure of HBV

HBeAg (a variant of the HBcAg) is a secreted protein expressed by HBV. HBeAg has 2main functional parts. The first is made up of 19 amino acid residues and is responsible fortransporting the protein to the endoplasmic reticulum. The other part is made of 10 residues and binds to HBcAg via an intra molecular disulfide bond which stabilizes both HBcAg and HBeAg.

HBeAg is important for the immune evasion properties of HBV. As previously mentioned, HBcAg assembles to form the virus capsid. The capsid is anicosahedr on composed of 120 copies of capsid protein homodimer. Each T=4 unitis composed of 4 HBcAg monomers (two dimers; AB and CD). The HBcAg capsid is extremely immunogenic, so induces both B-cell and T-cell immune responses; however, evidence suggests that those responses are not protective against an HBV infection. Due to its versatility and immunogenicity, HBcAg capsid scan be used as carriers for epitopesin vaccines.

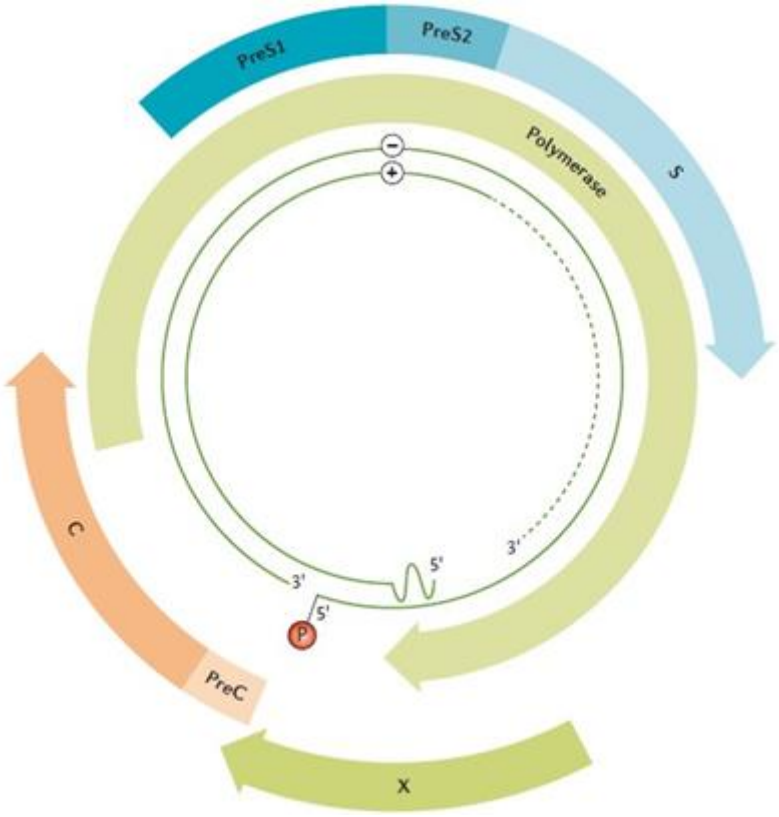

Figure 3: The genomic structure of HBV

Genomic structure of HBV

The hepatitis B virus (HBV) genome is organized in acircular form with the positive-strand DNA (with variable base length) forming the innercircleand the negative-strand DNA (completely circular) forming the outer circle. The four over lapping genes are Pf or translating polymerase, PreS1/PreS/Sf or hepatitis B surface antigen (HBsAg), PreC/C for core protein and X for HBx protein. The P protein has reverse transcriptase activity.The C and S open reading frames (ORFs) have extensions at their 5′ ends termed pre-C and pre-S.The pre-S region is divided into pre-S1 and pre-S2 domains, and translation of the S ORF leads tothe production of the large (L), medium (M) and small (S) HBsAg. Translation of the pre-C ORFresults in a secretory protein, hepatitis Be antigen (HBeAg), which is an accessory protein required establishing chronicity, whereas the CORF results in the capsid protein. HBx is required for establishment of infection and maintenance of active replication by inhibiting the host nuclear restriction factor, sister chromatid cohesion 5/6(SMC5/6). Over-expression of HBx has been shown to result incellular transformation via promiscuous trans activation. HBxAg is necessary for productive HBV infection in vivo and may contribute to the oncogenic potential of HBV.

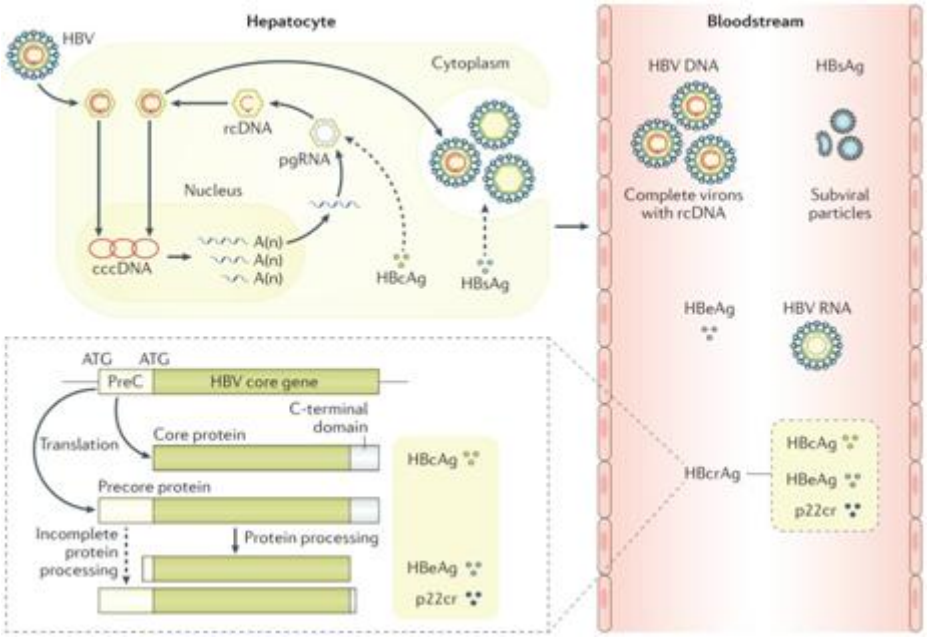

Figure 4: An overview of HBV mechanism and pathophysiology

HBV replication cycle and key viral markers

After viral entry into hepatocytes via the high affinity receptor sodium taurocholate co- transporting polypeptide, hepatitis B virus (HBV) relaxed circular DNA (rcDNA) enters the nucleus and is converted into covalently closed circular DNA (cccDNA) in the form of amini chromosome—the major transcriptional template of the virus. The transcription products are exported from the nucleus, with the larger pregenomic RNA (pgRNA) incorporated into replication complexes in the cytoplasm comprising the viral polymerase and core protein. Within these replication complexes, pgRNA is reverse-transcribed into HBVDNA, which can replenish cccDNA or undergo further packaging. The HBVDNA- containing capsid binds to the HBV surface proteins on the endoplasmic reticulum, is translocated into the lumen before exiting the hepatocytes through these cretory pathway and is then released as mature virus particles. mRNAs transcribed from cccDNA also produce various viral antigens. Except for cccDNA, all the other viral products(HBV rcDNA, HBV RNA, hepatitis B e antigen (HBeAg), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg) and 22 kDa pre core protein (p22cr)) are easilymeasurable inthe blood. The three antigens, HBcAg, HBeAg and p22cr (collectively known as hepatitis B core-related antigen (HBcrAg)), produced from translation of different starting codons of the preC coregene and differential protein processing afterwards. A(n), polyadenosine at the end of mRNAs.

Approved treatment agents

A timeline that shows the year of USFDA approval for individual hepatitis B virus (HBV) treatment agents. All the treatment agents have also beenapproved by the European Medicines Agency and in various Asian countries. The boxes in green refer to nucleoside or nucleotide analogues (NUCs), and the pale yellow boxes refer to interferon-

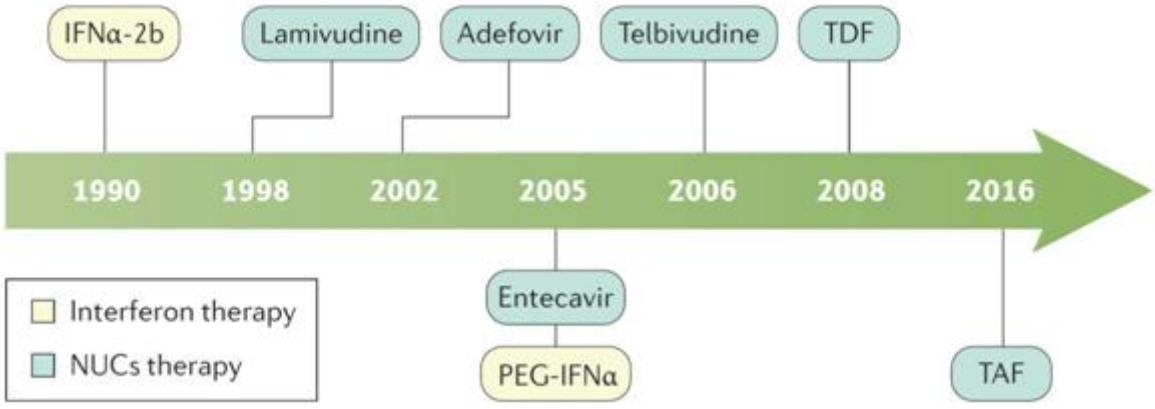

Figure 5: Approved treatment agents for chronic HBV infection.

based therapy. In 2018, the recommended first-line agents are pegylatedinterferonα-2a(PEG-IFNα), entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir ala fenamide (TAF).

Vaccination

The age of HBV infection is of vital importance in determining the risk of chronicity. The risk is > 90% for infants and children <1 year of age, 30% for children 1–5 years of age, and 0–2% for adults. Thus, mostchronic HBV infections are acquired through MTCT at the time of birth or during infancy and childhood.

Fact: Capsid-directed antiviral strategies: HBcAg can potentially be used as an antiviral target due to its role in the formation of capsids and the life cycle of HBV. Also, as capsidsh have no human omolog, they make great targets for therapeutic intervention. Research has shown that altering temperature and ionic strength of the HBcAg monomers can lead to the formation of aberrant non-capsid structures and trapped intermediates, which causes disruption to the capsid assembly. Taking advantage of this may be an effective antiviral method to combat HBV infections

Preventing HBV entry Ongoing replication and release of virusthat results in infection of new hepatocytes maintain chronic infection and the cccDNA pool11. In most patients, complete suppression of virusproduction is not achieved by NUC treatment. Therefore, combining anentry inhibitor with a replication inhibitor is an attractive proposal for reducing the cccDNA pool maintained by infection of new cells. There is also a drive to test this combination in patients co-infected with hepatitis D virus (HDV). HDV utilizes the HBV envelope and thus uses the same receptor for viral entry. HBV viral inhibitors could be of substantial benefit for individuals co-infected with HBV and HDV, and these patients have more severe disease than patients with HBV.

2. Conclusion

We should improve awareness of the disease, case finding, surveillance strategies and treatment optimization for the existing 257 million HBV chronically infected people. These challenging steps should be implemented without delay in all countries to reach thegoal set in May 2016 by the WHO: the elimination of viral hepatitis as a public threat, with 90%reduction of new hepatitis infections and 65% reduction in mortality by 2030. Although health-care workers, health-related statutory personnel, paramedics and patient groups are actively involved in the first three aspects, HBV disease clinicians and researchers are the key persons to improve the treatment for HBV disease.

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