REVIEW ARTICLE

HEPATITIS B VIRUS, STRUCTURAL BIOLOGY, GENOTYPING, AND PATHOGENESIS

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ABSTRACT

Understanding the structural biology, genotyping, and pathogenesis of HBV is crucial because it is a significant health risk that affects people all over the world. The four structural proteins that the HBV genome codes for are crucial to the pathogenesis of the virus. HBV genotypes vary by region, and these genotypes may respond to antiviral medication and vaccinations differently. Both molecular and serological assays are capable of detecting HBV infection. Chronic infection and antiviral therapy must be closrzely monitored in the management of HBV infection. HBV infection can be prevented by receiving the HBV vaccine, which is both reliable and secure. HBV genotypes, genetic polymorphisms, and relationships with leukomonocytes will be the main topics of future study.

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INTRODUCTION

The Hepatitis B virus (HBV) poses a significant risk to public health globally as the ninth leading cause of death worldwide.[1] A sizable reservoir of chronic carrier patients makes eradication efforts challenging despite the availability of safe and effective prophylactic vaccines. HBV infection is very common, and non-immune people have a greater risk of infection if the source is positive for the hepatitis B e antigen (HBeAg).[2] The virus can cause acute and chronic hepatitis, liver cirrhosis, liver cancer, and even death. Asians are disproportionately affected by HBV, accounting for up to 75% of all carriers.[3] Due to their propensity for mutation, drug-resistant and vaccine-escape mutants of HBV pose serious clinical and public health risks. Understanding HBV Structural Biology, Genotyping, and Pathogenesis is crucial for developing novel antiviral drugs and vaccines, understanding the epidemiological relationships between different virus strains, identifying the mechanisms by which HBV causes liver damage and hepatocellular carcinoma, diagnosing and following HBV infection, and developing novel treatment regimens. Therefore, it stands to reason that HBV research is crucial in the fight against hepatitis B virus infection.

STRUCTURAL BIOLOGY OF HBV

The enveloped DNA genome of the pararetrovirus known as the hepatitis B virus (HBV) is about 3,200 base pairs.[4] It has four open reading frames that partially overlap and encode the envelope, core, polymerase, and X proteins.[5, 6] Hepatitis B surface antigen (HBsAg)-containing external envelope and nucleocapsid, which surround partially double-stranded circular DNA, make up the virion. Hepatitis delta virus (HDV) particles, mature HBV virions, and empty subviral particles can all be put together by the envelope proteins. The hepatitis delta antigen (HDAg), the only known virus-encoded protein, and the hepatitis B surface antigen outer envelope are both found in the HDV virion, which is a small, single-stranded, circular RNA molecule of about 1.7 kb. The structure, molecular size, and biological traits of HBV are shared by the woodchuck hepatitis virus (WHV).[7, 8]

The pathogenesis of HBV infection depends heavily on the structural proteins of HBV, including the core and envelope proteins. Hepatocellular carcinoma can result from the core protein (HBc) disrupting several pathways associated with liver carcinogenesis, including those connected to cell migration, proliferation, apoptosis, and metabolic processes (HCC). On the other hand, HBx has a pro-apoptotic function that aids in liver pathogenesis and has been strongly linked to HBV-associated liver pathogenesis. Cell death is caused by cytosolic calcium levels being elevated by HBx's interactions with cellular proteins, such as the anti-apoptotic proteins Bcl-2 and Bcl-xL. This promotes HBV viral replication and pathogenesis. Three different viral particles can be assembled by the envelope proteins: mature HBV virions, mature subviral particles, and coexisting HDV particles that rely on their envelope proteins for virus assembly. HBV pathogenesis is aided by HBx's interaction with lysine methyltransferase SMYD3, which activates activator protein 1.[9-11]

Globally, there are distinct regional distributions of HBV genotypes. While genotype B is more common in East and Southeast Asia, genotype A is more common in Europe, North America, and Africa. While genotype D predominates in the Mediterranean region, the Middle East, and South Asia, genotype C is more common in Japan, Korea, and China. While Central and South America have genotype F, West Africa has genotype E. Although uncommon and not associated with any particular geographic area, genotype G frequently co-infects with other genotypes in high-risk populations.[12-14] The most prevalent genotype in Pakistan is genotype D, which is followed by genotype A and mixed infections of genotypes A and D. The distribution of genotypes varies by region, with genotype D being more prevalent in the provinces of Punjab and Sindh and genotype A being more prevalent in Khyber Pakhtunkhwa. Since different genotypes may react differently to antiviral therapy and vaccines, understanding the distribution of the HBV genotype is essential for creating effective treatment plans and vaccines.[15, 16]

PATHOGENESIS OF HBV

Both direct and indirect mechanisms underlie the development of chronic hepatitis, cirrhosis, and HCC due to HBV infection. HCC and liver cirrhosis are primarily caused by immune-mediated hepatocyte damage and chronic inflammation. HBx and other HBV-encoded proteins are crucial for cell proliferation, anti-apoptosis, apoptosis, and transformation. Liver damage can also result from problems with the endoplasmic reticulum and mitochondrial homeostasis. Defective HBV surface antigens advance HBV-associated liver diseases because they play a crucial role in HBV-related pathogenesis. The progression of chronic HBV to cirrhosis, end-stage liver disease, or HCC is sped up by co-infection with HIV and HBV. Therefore, for prevention and clinical intervention, it is critical to understand the pathogenesis of HBV-induced liver damage and HCC.[9, 17]

The main factor contributing to hepatocyte damage in HBV infection is immune-mediated mechanisms. The progression of liver disease can be predicted by the frequency and intensity of hepatitis flare-ups. The strongest associations between HBV persistence and genes have been found within the HLA genes, which play a variety of roles in immune mechanisms. HBV-induced HCCs can form in non-cirrhotic livers, proving that HBV directly contributes to liver transformation by triggering both generic and aetiology-specific oncogenic pathways, as well as the host immune system and chronic liver inflammation. A small percentage of people with chronic HBV infection develop neuropathy, and immune complex deposition in nerve or blood vessel walls may be the underlying pathogenesis of HBV-associated neuropathy syndromes.[18-20]

HBV INFECTION DIAGNOSIS AND MONITORING

The diagnosis of HBV infection can be made using molecular and serological assays. While molecular assays, such as polymerase chain reaction (PCR), which have high specificity and sensitivity and are used to identify occult HBV infections, detect HBV DNA, serological assays, such as those for HBV surface antigen (HBsAg), and other serological markers. Monitoring the efficacy of antiviral therapy and spotting the early emergence of antiviral drug resistance are both possible through the quantification of HBV DNA. Molecular diagnostics are also being used on liver tissue that has HBV infection. Additional options for tracking and forecasting treatment effectiveness may be offered by the use of molecular techniques to quantify intrahepatic HBV DNA and other significant HBV replicative intermediates. Testing for qualitative HBsAg has long been used as a diagnostic indicator for people with HBV infection in clinical settings. To distinguish patients during the course of HBV infection and to keep track of therapy, quantitative detection of HBV DNA and HBsAg can be used. There are several rapid diagnostic tests (RDT) for HBsAg, but some of them have low sensitivity. In conclusion, serological and molecular assays, including PCR, are used in the laboratory to detect HBV DNA and measure viral load. These assays can be used to track the success of antiviral therapy and identify the early stages of antiviral drug resistance.[21, 22]

Hepatitis B virus (HBV) S gene mutations can cause immune escape and the coexistence of HBsAg and

hepatitis B virus surface antibody (HBsAb). The sensitivity of immunodiagnosis, particularly for the detection of HBsAg, depends heavily on the genetic variability of the S gene. However, it is unclear how the S gene's genetic variability affects HBV diagnosis. Several studies have looked into how the S gene varies concerning the antiviral treatment and the emergence of hepatocellular carcinoma (HCC). For instance, one study discovered that 11-12% of lamivudine (3TC)-resistant patients had variable combinations of secondary/compensatory mutations, and some of these patients also had mutations that altered the S protein's antigenicity.[23, 24] Another study discovered that complex variability of the viral mutants as detected by PCR was related to nonresponse to antiviral therapy. Therefore, changes to the HBV S gene region may have an impact on immune recognition, infection, secretion, packaging, and other processes. Additionally, mutations in the S gene region can alter the antigenicity of the S protein and impact the sensitivity of immunodiagnosis, particularly for the detection of HbsAg.[25, 26]

The management of hepatitis B virus (HBV) infection depends on careful observation of antiviral therapy and chronic infection. Antiviral therapy aims to stop viral replication and delay the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and death as a result of liver damage. To assess the viral, host, and pharmacological aspects of HBV treatment, laboratory testing is crucial. Patients must also be watched closely both during and after therapy to ensure their safety and gauge the viral response. Hepatitis B surface antigen (qHBsAg) quantitative testing in conjunction with HBV DNA testing may be helpful in the management of chronic HBV disease and provides data for clinicians to track patient responses to antiviral therapy. For the monitoring of viral load in chronic hepatitis B and C, sensitive and quantitative assays are needed. When using nucleoside analogues to diagnose HBV resistance, viral genome mutations must be found. The quick development of particular inhibitors that might favour drug-resistant mutants may also be helpful for anti-HCV therapy. Laboratory testing is essential for tracking the effects of both antiviral therapy and chronic infection, and quantitative qHBsAg testing in conjunction with HBV DNA testing gives clinicians important data to track how well patients are responding to antiviral therapy.[27, 28]

VACCINATION AND PREVENTION OF HBV INFECTION

Hepatitis B virus infection can be controlled and possibly stopped through the proper use of hepatitis B vaccines. In regions where childhood transmission is the main cause of chronic HBV infections, strategies for the efficient use of the hepatitis B vaccine have been developed and are being put into action. However, current vaccination strategies have not been completely effective and have not fully taken into account the complex epidemiology of HBV infection in areas with "low" rates of HBV infection. The disease burden has significantly decreased as a result of the routine vaccination programmes for newborns, infants, and adolescents in about 180 countries. In some circumstances, such as after a single acute exposure, in babies born to infected mothers, and in people undergoing liver transplantation, passive immunisation with particular HBV immunoglobulins is advised. The HBV vaccine is a safe and effective first human vaccine that uses a viral antigen from infected individuals. The best efficacy for preventing HBV infection comes from a combination of both passive immunisations with hepatitis B immunoglobulin (HBIG) and active immunisation with the HBV vaccine.[29-31]

Hepatitis B vaccines are both effective and safe in preventing HBV infection. Hepatocellular carcinoma and HBsAg carrier rates have been successfully decreased by recombinant yeast-derived HBV vaccines. Pre-S/S epitopes expressed in mammalian cells are present in new-generation recombinant HBV vaccines that have the potential to be used in specific risk groups. Around 180 countries have adopted the World Health Organization's universal vaccination recommendations for newborns, young children, and teenagers. Depending on the vaccine being used, the first dose should be administered within 24 hours of birth and should be followed by two or three additional doses. Adults at high risk of infection should also get the vaccination.[27, 32, 33]

CONCLUSION

The distribution of HBV genotypes, which are related to treatment response and drug resistance, will be a focus of hepatitis B virus (HBV) research in the future. It is necessary to conduct more research on the associations between HBV genotypes and disease severity, prognosis, and disease progression. The relationship between IL28B gene genetic polymorphisms and leukomonocyte in HBV-infected people may offer important insights into the genetic pathogenesis of HBV. The monitoring of chronic hepatitis B treatment could be enhanced by the development of novel DNA sequencing techniques for HBV genotyping and drug-resistant mutation detection.

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