Hepatitis B Virus Genetic Variability and its Clinical Significance

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Hepatitis B virus (HBV) infection is a worldwide health problem and the major cause of chronic hepatitis, cirrhosis as well as hepatocellular carcinoma (HCC). HBV is an enveloped virus, containing a 3.2 kb partially double-stranded DNA genome that is replicated via an RNA intermediate using its own encoded reverse transcriptase (RT). The HBV RT does not have proofreading or editing activity, therefore, together with its enormous daily virion production, errors inevitably occur during replication in long-term infected patients. Particular selection pressures, both endogenous (host immune clearance) and exogenous (vaccine or antivirals), strongly influence the predominant HBV quasispecies and their biological characteristics in an infected individual at a given time point. The mutation of HBV would bring a series of new problems to the prevention, diagnosis and treatment of chronic hepatitis B.

Current studies have showed that mutations in the genome exert a substantial effect on the replication capacity of the virus. Immune and antiviral selection pressures result in vaccine/immunoglobulin escape mutants and antiviral resistant variants. Viruses encoding changes associated with antiviral resistance often have reduced replication in vitro, but the accumulation of additional compensatory mutations helps restore viral fitness. Additionally, in our study, we found that HBV genome variation occurred in the hepatocyte nuclear factor (HNF) 4 and/or HNF3 binding sites may significantly change the capacity of viral replication.

The mechanisms determining the emergence of viral variants in response to immune selection may be important in considering possible therapeutic interventions designed to prevent their pathophysiological consequences. Viral variants containing two nucleotide substitutions (A1764T and G1766A) in the proximal nuclear hormone receptor binding site in the nucleocapsid promoter are very common variants identified from patients who have seroconversion from HBeAg to anti-HBe antibody status. The results of our study indicate that replication of wild type and variant viruses can be differentially regulated by nuclear hormone receptors, and this may be important in the selection of specific viral variants as a result of an antiviral immune response. Chronic HBV infection is a dynamic state involving interaction between the virus, the hepatocytes and the immune cells of the host. The role of continuing HBV replication in the hepatic necroinflammatory response leading to hepatocarcinogenesis has been shown. Several HBV mutant strains including mutations in precore, core promoter and deletion mutation in pre-S/S genes have been reported to be associated with the pathogenesis of progressive liver disease, including hepatitis flare, decompensation, liver cirrhosis and hepatocellular carcinoma (HCC).

The goal of therapy in patients with chronic hepatitis B is rapid viral suppression and long-lasting maintenance of undetectable levels of serum HBVDNA. Nucleoside/nucleotide analogues rapidly are becoming the treatment of choice for patients with Chronic Hepatitis B. The major draw back of this treatment is the considerable risk of developing antiviral drug resistance associated with progressive disease, which occurs most frequently in lamivudine-treated patients, but also has been shown for other agents (eg, adefovir, telbivudine and entecavir) evaluated in long-term studies. Location of the major antiviral drug-resistant mutations associated with LMV, LdT, ADV, TDF, and ETV have been identified in recent years. Antiviral therapy should be modified as soon as resistance is detected.

Therefore, it is necessary to monitor the occurrence and development of HBV variations and the relationship between variability and clinical outcome dynamically. Enhancing the biological characteristics research of hepatitis B virus would help us further understand the effect of mutations on viral replication capacity, and better understand the roles of mutations in drug-resistance and disease prognosis.

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