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Host Genetic Factors in Hepatitis B Virus Infection

Runu Chakravarty

ICMR Virus Unit, Kolkata GB-4, 1st Floor ID & BG Hospital Campus, 57 Dr S C Banerjee Road, Kolkata 700 010, West Bengal, India

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ABSTRACT Worldwide about 350 million people are chronic carriers of the hepatitis B virus (HBV). The infection can cause acute and chronic liver disease including cirrhosis and hepatocellular carcinoma (HCC). Hepatocellular injuries of HBV infection are predominantly immune-mediated and a complex ill understood interplay of virological factors, host immunological factors and genetic factors as well as the environmental factors determine the clinical outcome. There is strong evidence in HBV infection that host genetic factors play a major role in determining the outcome of infection. Among different approaches that may be used to determine the specific genetic factors involved, the principal method which has been used to date, is the disease association study. The association of the MHC class II alleles and interleukin-10 promoter polymorphism has been demonstrated to influence the outcome of these infections. The MBP polymorphism has also been found to be involved in chronic infection in some population groups but not in others. Since genetic interactions are complex, it is unlikely that a single allelic variant is related to HBV resistance or susceptibility. The collective influence of several single nucleotide polymorphisms (SNPs) or haplotype(s) might determine the natural combinational effect against HBV. The future study including the multi-cohort collaboration will be needed to clarify these preliminary associations and identify other potential candidate genes.

INTRODUCTION

Despite having safe and efficacious vaccine hepatitis B remains one of the one of the most common infectious diseases of the world today. According to WHO fact sheets, of the 2 billion people who have been infected with the hepatitis B virus (HBV), more than 350 million have chronic infections in the world at present. Chronic hepatitis B infection can cause a broad spectrum of diseases, ranging from asymptomatic HBV carriers to acute hepatitis, chronic hepatitis, liver cirrhosis and primary hepatocellular carcinoma and leads to high rate of morbidity and mortality. Although most carriers will not develop hepatic complications from chronic hepatitis B, 15% to 40% will develop serious sequelae during their lifetime, which accounts for 1 million deaths due to HBV infection each year (Purcell 1993). The reasons for the variations in the natural history of HBV infection are not fully understood, but are mainly determined by 1) virological factors like viral load, genotype and genetic divergence due to viral mutations, 2) Immunological factors including the innate and adaptive immune response against viral infections. The mutations in the in HBV epitopes recognized by HBV specific CTLs may cause both humoral and virus specific immune responses to loose their ability to efficiently control the virus. 3) Host genetic factors, and 4) environmental factor (Lino 2002).

In recent years extensive work has been done on virological and immunological factors of HBV infection, but the studies on the role of host genetic factors on the clinical outcome of HBV infection is still in its infancy. This review focuses on the recent development in the study of human genetic alleles associated with chronic hepatitis B virus infection.

There is strong epidemiological evidence in HBV infection that host genetic factors play a major role in determining the outcome of infection. Among the infected adults 90-95% of the adults can clear the virus and only 5-10% of the adults become chronic carriers. Among the carriers 20-30% develops liver cirrhosis and about 5% develop hepatocellular carcinoma after being HBV carrier for long. On the other hand, babies of infected mothers acquire infection perinatally and develop chronicity in 70-90% cases. However, even in a family, all of the high-risk individuals do not develop disease. Studies on Chinese twins have demonstrated that the degree of concordance for hepatitis B surface antigen status was significantly higher in monozygotic twins than in dizygotic twins. There are geographical variations of HBV prevalence among the different countries. Immigrants retain the HBV prevalence rate of their country of origin. All of these signal the role of human genetic factors on

the progress of liver disease. Thus studies on human genetic factors may provide crucial information on disease susceptibility, outcome of infection and therapeutic response (Thio et al. 2000).

Two strategies are currently being used to identify host genetic factors associated with disease phenotype (Lander and Schork 1994). These include genome-based scans and search for candidate genes. Since both chemokine receptor and HLA genes play major roles in host immune response to viral infection, they are among the first HBV candidate genes screened.

STUDIES ON MHC POLYMORPHISM

Proper antigen presentation with the help of MHC II to the T-helper cells is crucial for HBV clearance (Thursz 1997). A number of studies have examined the role of MHC II polymorphism in the outcome of HBV infection. In a Gambian as well as in a European population, HLA-DRB1*1302 was associated with spontaneous clearance of infection. Thio et al examined the DQA180501, DQB180301 and DQA1-DQB1 haplotypes and found the haplotype cluster of DQA1*0501-DQB1*0301-DQB1*1102 had a significant association with viral persistence (Thio et al. 1999). However, Zavagila et al reported that no correlation could be associated with the clearance of HBV and HLA phenotypes (Zavaglia et al. 1996). Diepolder et al reported that HLA DR13 allele is less frequent in patients with chronic hepatitis B than in healthy controls or in subjects with self-limiting hepatitis B (Diepolder et al. 1998). A recent study among Chinese patients showed HLA-DRB1*0301, HLA-DQA1*0501 and HLA-DQB1*0301 are reported to be closely related with susceptibility to chronic hepatitis B, and HLA-DRB1*1101/1104 and HLA-DQA1*0301 are closely related with resistance to chronic hepatitis B (Jiang et al. 2003). In these patients rapid progression to chronic hepatitis B is rare, suggesting that patients with HLA-DR13 can mount a more vigorous CD4+T cell response during acute HBV infection. Only one recent study on HLA class I polymorphism has been reported. It shows that a single class I allele, A*0301 was associated with viral clearance in addition to the class II allele DRB1*1302, among Caucasian patients. B*08 was associated with viral persistence. Both the B*08 haplotype and DR7, which forms a haplotype with B*44-Cw*1601, have been associated with non-response to the HBV vaccine. The associations with class I alleles are consistent with the role of HLA class I molecules in mediating cytotoxic-T-cell response through cytolytic and noncytolytic mechanism (Chloe et al. 2003). A study carried out among Indian patients supported negative association of DRB1*13XX to persistence of HBV and possible role of DRB1*11XX and DRB1*15XX in development of chronic HBV hepatitis due to persistence of HBV (Amarapurkar et al. 2003).

Cytokines and Chemokines

Cytokines play an important role in defense against viral infection, indirectly through determination of the predominant pattern of the host response, and directly through inhibition of viral replication (Fiorentino et al. 1991). Variation in cytokine release is mainly associated with polymorphism within or near the gene. Several pro-inflammatory cytokines such as Th1 cytokines (including IL-2 and IFN-γ) and tumor necrosis factor-alpha (TNF-α) have been identified as participating in the viral clearance and the host immune response to HBV. In contrast, the Th2 cytokine IL-10 serves as a potent inhibitor of Th1 effector cells (Fiorentino et al. 1991; Knight et al. 1999; Hajeer et al. 2000; Miyazoe et al. 2002). Initial studies in Gambian population suggested that a point nucleotide substitution at position –308 (with respect to the transcription initiation site) be accompanied by an adverse outcome of HBV infection in which an allele associated with raised TNFα secretion correlated with persistent infection (Tibbs et al. 1996; Thursz et al. 1999). In a European population a second polymorphism at position -238 in the promoter region was associated with outcome although in this study, higher TNF-α secretion correlated with clearance of infection (Hohler et al. 1998). On the other hand, Miyazoe *et al* while analyzing the distributions of TNF-α and IL-10 promoter SNPs in Japanese HBV-infected patitents found that the -819T and -592A wild-type alleles in the IL-10 gene promoter were significantly more common in asymptomatic carriers than in patients with chronic progressive liver diseases (Miyazoe et al. 2002). These results suggests that inheritance of the IL-10 gene promoter polymorphisms is relevant to progression in chronic HBV infection, perhaps

due to decreased IL-10 production induced by -819T and -592A haplotype allele. Thurz found that an allele associated with high levels of IL10 secretion was associated with spontaneous elimination of HBV infection (Thursz et al. 1996). While studying the relationships between polymorphisms of interleukin-1B (IL-1B) promoter region -511C/T and interleukin-1 receptor antagonist gene (IL-1RN) and susceptibility to chronic hepatitis B in Chinese population, Zhang et al. (2004) reported an association between polymorphisms of the promoter region -511C/T of IL-1B and IL-1RN intron 2 and chronic hepatitis B virus infection.

Polymorphism of Mannose Binding Protein (MBP)

MBP is a lectin that binds nonspecifically to a non-human sugar chain and opsonizes the pathogen. The middle surface protein of HBV envelop contains a mannose rich oligosaccharide with potential MBP site. Thomas et al showed that 27% of Caucasian population chronically infected with HBV were homozygous or heterozygous with codon 52 mutant allele compared with only 11% of acute infection or 4% of control carried the wild type allele , suggesting association with HBV persistance with codon 52 mutant allele (Thomas et al. 1996; Yuen et al. 1999). The higher frequency of mutants among HBV patients than among controls suggests that mutation possibly leads to failure of opsonisation and subsequent phagositosis of HBV. MBP codon 54 polymorphism was reported to be associated with symptomatic persistant HBV infection in Chinese patients. Among the Caucasian and Gambian patients of Germany, these MBP polymorphisms were not associated with chronic infection (Hohler et al. 1998).

Macrophase/Monocyte Inactivation

The vitamin D receptor is expressed on monocytes and lymphocytes and stimulation of this receptor is thought to influence the immune response. Bellamy et al studied two known vitamin D receptor gene polymorphism in Gambian HBV infected patients (Bellamy and Hill 1998). An allele of the vitamin D receptor that increases transcriptional efficiency has been associated with control of viral replication in HBV infection.

FUTURE STUDIES

The process of identifying the host genetic contribution to the outcomes of HBV infection has just began and it appears the collective influence of several SNPs and/or haplotype(s) may exert the natural combinational or synergistic protection against HBV, since genetic interactions are complex (Dean et al. 2002). Future genetic epidemiology strategies and dense genome-wide search, together with the growing availability of candidate alleles and sequence information will contribute to identifying genes associated in HBV infection. However, the result will depend upon various factors including the viral phenotypes, population traits, and accurate measurement of environmental factors and previous knowledge of HBV infection. Because of this, future study including the multicohort collaboration will be needed to clarify these preliminary associations and identify other potential candidate genes (Abel and Dessein 1998). The accumulated information is likely to provide prognostic markers for the outcome of these infections, in addition might also provide a novel rationale for new methods of diagnosis and therapeutic strategies (Griffiths 2002).

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