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The Influence of Human Leukocyte Antigen and IL-10 Gene Polymorphisms on Hepatitis B Virus Outcome

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ABSTRACT

Context: The clinical outcome of hepatitis B virus (HBV) infection is variable, ranging from spontaneous recovery to an inactive carrier state, chronic hepatitis, occult HBV infection, liver cirrhosis, or hepatocellular carcinoma.

Evidence Acquisition: This variable pattern and clinical outcomes of the infection were mainly determined by virological and host genetic factors. Since the most of host genetic factors associated with HBV infection have currently focused on human leukocyte antigen (HLA) associations and interleukin (IL)-10 gene polymorphisms, this review focuses on the recent progresses in these issues to provide prognostic markers for the outcome of HBV infection.

Results: A study on serum levels of IL-10 in occult HBV infected patients reported that the higher level of IL-10 production may suppress function of the immune system against HBV in patients with occult HBV infection (57). IL-10 promoter polymorphism at position -592 is associated with susceptibility to occult HBV infection.

Conclusions: Findings of this study suggest that the host HLA polymorphism is an important factor in determining outcome of HBV infection but regarding IL-10 gene promoter polymorphisms, we are still have a long way to achieve a definite conclusion.

▸ *Implication for health policy/practice/research/medical education:*
This article provides prognostic markers including HLA and IL-10 polymorphisms for determining the outcome of HBV infection.

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1. Context

Hepatitis B virus (HBV) infection is a major public health problem worldwide (1). HBV is transmitted via contact with infected body fluids, including blood, saliva, and semen (2). The outcome of HBV infection is highly variable, ranging from asymptomatic disease culminating in the spontaneous elimination of infection to persistent infection that can lead to occult HBV infection (OBI), cirrhosis, liver failure, or hepatocellular carcinoma (3, 4). The precise mechanisms leading to these various outcomes are not yet clearly defined, but environmental, immunological (such as the innate and adaptive immune responses against viral infection), virological (such as genotype and genetic divergence mutants), and host genetic factors are

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considered as important factors contribute in HBV infection outcome (3, 5-7).

It has been perceived that host genetic factor is the critical component in determining the outcomes of HBV infection (1). The most important host genetic factors associated with HBV infection outcome have currently focused on human leukocyte antigen (HLA) and cytokines associations (8). Associations between HLA polymorphism and disease susceptibility as well as disease resistance have been well investigated, especially in autoimmune and metabolic diseases (9, 10). Besides extensive allele diversity in HLA is associated with susceptibility or protection of HBV infection in different ethnic populations (11).

Major histocompatibility complex (MHC) gene products are vital in regulating several antiviral immune reactions. In addition, genetic factors controlling host immune response could play an important role in determining infection outcome. Alloantigens are taken up by antigen-presenting cells, which process them and re-express the antigens on the cell surface along with HLAs to be recognized by the T-cell receptor. The polymorphisms of HLA alleles may cause significant changes in the presentation of antigen to T cell receptor, which in turn affects immune response (12, 13). Several proinflammatory cytokines such as T helper (Th) 1 cytokines (including interleukin (IL)-2 and interferon (IFN)-gamma) have been identified to participate in the process of viral clearance and host immune response to HBV. In contrast, the Th2 cytokine (IL-10) serves as a potent inhibitor of Th1 effector cells in HBV diseases. Polymorphisms in the regulatory regions of the cytokine genes may influence their expression. Therefore, as genetic predictors of disease susceptibility or clinical outcome, the polymorphisms of cytokine genes are potentially important (8, 14).

In the last decade, the virological and immunological factors associated with HBV infection outcome have been extensively studied, but the examination of the relationship between host genetics and HBV resistance is still scarce (8, 15, 16). Since the most of host genetic factors associated with HBV infection have currently focused on HLA associations and IL-10 gene polymorphisms, this review focuses on the recent progresses in these issues.

2. Evidence Acquisition

2.1. HLA Class I and II Alleles

Highly polymorphic HLA gene (a cluster of closely linked genes including class I, class II, and class III) is located on the short arm of chromosome 6 (17) and play a critical role in modulation of immune response. Effective presentation of viral antigens to CD4+ T cells and CD8+ T cells by HLA class II and I molecules respectively, is the key regulation of optimum immune response against viral infection and further dictates of viral clearance or persistence (11, 18). Due to the specific antigen presenting function of HLA in immune responsiveness, the contribution of HLA to the outcome of HBV infection has been studied in different populations. However, data have shown some inconsistencies with regard to HLA effects on HBV clearance or persistence in different ethnic and racial groups (7).

Both HLA class I and II alleles have been associated with the outcome of HBV infection, although the majority of studies have focused on the associations between HLA class II alleles and HBV infection (19, 20). Chen *et al.* (21) showed that allele frequencies of HLA-B8, DR3, A30, and DQA1*0501 were high in patients with chronic hepatitis B (CHB) infection, suggesting that these alleles are associated with CHB. A study in African-American adults reported that HBV persistence was correlated with DQA1*0501 and DQB1*0301 alleles found in a common DQA1-DQB1 haplotype (22). Thio *et al.* (18) reported that HLA-B*08 was associated with viral persistence.

The data of Yang indicated that HLA-DRB1*03 and HLADRB1*07 were related to susceptibility to chronic HBV infection, and that DRB1*15 was negatively related to the persistence of chronic HBV infection among people in northwestern China (1), whereas Meng *et al.* (23) showed that HLA-DRB1*1201 is associated with protection against chronic hepatitis B, and HLA-DR9 and DQ9 are associated with chronicity of HBV infection in Zhejiang Province, China. A study in northern Chinese patients showed that susceptibility to chronic hepatitis B was strongly associated with HLA-DRB1*10 allele (24). The findings of Jiang suggested that HLA-DRB1*0301, DQA1*0501, and DQB1*0301 are closely associated with the susceptibility to CHB, and HLA-DRB1*1101/1104 and DQA1*0301 are related to resistance to CHB (26). Han *et al.* (25) reported that HLA-DRB1*06, -DRB1*08, and -DRB1*16 may be associated with chronicity of HBV infection, and HLA-DRB1*07 with protection against HBV infection.

Hwang *et al.* (26) reported the associations between HLA-A33 or DR7 and HBV chronicity. Their study strongly showed that a combination of these two antigens has an additive effect on HBV persistency. Another Korean study found that the presence of DRB1*0701 and DQB1*0301 was associated with chronic HBV infection (7). In a study involving subjects from eastern Turkey, frequencies of HLA-B35, -CW4, -DQ2, and -DQ8 were markedly higher in chronic HBV group than those in spontaneously recovered group (3). A study by Ramezani *et al.* (19) in Iran showed that the frequency of HLA-A*33 allele was higher in HBV persistent group whereas the frequency of the DRB1*13 allele was higher in HBV recovered group. They reported that HLA-A*3303 and DRB1*1301 were predominant allelic subtypes related to HBV infection outcomes (27).

Thursz *et al.* (20) studied both children and adults in Gambia, and found that MHC class II allele HLA-DRB1*1302 was more frequent in individuals that had cleared the infection than in those presenting persistent infection. Cotrina and Thio *et al.* (18, 28) also showed that HLA-

DRB1*1301 and -DRB1*1302 alleles were associated with the clearance of HBV infection and protected people against chronic hepatitis B. Karan and Diepolder *et al.* (29, 30) also observed that HLA-DR13 was present at a higher ratio in the group capable of creating spontaneous HBV antibody, suggesting that HLA-DR13 is associated with a self-course of HBV infection. Ahn *et al.* (31) reported that HLA-DR6 and especially HLA-DR13 are associated with the elimination of the HBV infection. In a Taiwanese study, HLA-DRB1*0406 was associated with recovery from HBV infection in Han Chinese, as was HLA-B*4001 in Aborigines (32). Studies investigating HLA association with hepatitis B infection outcome are summarized in *Table 1*.

2.2. IL-10 Gene Polymorphisms

Cytokines, mainly secreted by lymphocytes and monocytes, serve as immune response molecules with various physiological functions that regulate immunologic, inflammatory, and reparative host responses . T cell derived cytokines are important in the host immune response (33). Activated T lymphocytes are divided into two functional subsets, Th l and Th2 cells, on the basis of cytokines that they produce (33). Thl cytokines, including IL-2, IFN-gamma, and tumor necrosis factor (TNF)-α, are involved principally in cell-mediated immunity and play a crucial role in protection against intracellular pathogen (33, 34), whereas Th2 cytokines, including IL-4, IL-5, and IL-10, mostly regulate antibody mediated immunity; their effects can be beneficial against extracellular agents but can be associated with progressive disease by intracellular pathogens (34, 35). Interleukin-10 is one of the critical modulators which is produced by activated macrophages, T regulatory, B regulatory, and Th2 lymphocytes and inhibits expression of other proinflammatory cytokines such as IFN-gamma, IL-2, and TNF-alpha in Th1 cells (36). IL-10 influences natural history of HBV infection and other viral diseases such as Epstein-Barr, herpes zoster, HIV, and hepatitis C (37-39). The levels of IL-10 production determine immune regulation and the balance between inflammatory and anti-inflammatory responses (4).

There are some evidences showing that the capacity of IL-10 production is a major genetic component which has an association with development and progression of HBV infection (40-42). This has been ascribed to polymorphisms within the regulatory regions or signal sequences of this cytokine gene which have shown to be important in the susceptibility to inflammatory disease (8, 41), responsiveness to HBV vaccination (43), HBeAg seroconversion in HBV carriers (44) and HBV-related hepatocellular carcinoma (45, 46). In IL-10 gene promoter region, three biallelic polymorphisms were determined at positions -1082, -819, and -592 (8). The carriers of -1082 G/G genotype are high IL-10 producers, the -1082 G/A carriers show intermediate production of IL-10, and the -1082 A/A genotype is associated with low IL-10 production. Polymorphisms at position -819 and -592 have no independent influence on IL-10 production (47).

IL-10-819 T and C alleles were completely in linkage disequilibrium with IL-10-592A and C alleles, respectively. The -592A allele was exclusively associated with the-1082A allele. These result in three different haplotypes: GCC, ACC and ATA (48). Miyazoe *et al.* (41) analyzed the distributions of IL-10 promoter single nucleotide polymorphisms (SNPs) in Japanese HBV-infected patients and found that the -819T and -592A wild-type alleles in IL-10 gene promoter were significantly more common in asymptomatic carriers than in patients with chronic progressive liver diseases, suggesting that inheritance of 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 alleles. Turner *et al.* (48) also indicated that A/A genotype at position -592 in IL-10 gene promoter, which was associated with lower IL-10 levels, had a modest effect in HBV clearance. Shin *et al.* (46) reported that in high IL-10 producers, chronic HBV infection progression accelerated. In contrast Cheong *et al.* (49) reported that C/C genotype frequencies at position –592 in IL-10 gene promoter were significantly higher in HBV clearance group than in HBV persistence group. They suggested that the carriers of IL-10-592 C/C (high IL-10 producers) were more likely to clear HBV spontaneously compared to those carrying IL-10-592A allele (low IL-10 producers).

A meta analysis conducted by Lu *et al.* (50) indicated that the G and A alleles in IL-10-1082 were not associated with HBV infection in Asian population, whereas another meta analysis in Chinese pooled population reported a relationship between IL-10-1082G/A polymorphisms and persistent HBV infection and indicated that there was significantly reduced risk of persistent HBV infection with IL-10-1082A/A genotypes.

3. Results

The results of this study suggest that carriers of IL-10-592A allele were more likely to clear HBV spontaneously (2). Another study in African Americans also showed that HBV infection outcome was influenced by proximal promoter SNP IL10-1082 (51). Gao *et al.* (4) showed that IL-10-1082 A/A was associated with an increased risk, but-1082 A/G with a reduced risk of persistent HBV infection. In an investigation by Peng *et al.* (45) patients with intermediate producer genotypes or haplotypes of IL-10 had more ability to produce anti-HBe than those with low producer genotypes or haplotypes, so they were usually associated with a covert mode of HBeAg seroconversion. Another study by Wu *et al.* (52) showed that patients with G/G genotype in the –1082 promoter area of IL-10 gene underwent HBeAg seroconversion at a significantly younger age than patients who had G/A and A/A genotypes. They suggested that a polymorphism at the –1082 locus of IL-10 gene promoter may modulate production of IL-10, and G/G genotype is considered as a high-production geno-

Table 1. Studies Investigating HLA Association With Hepatitis B Infection Outcome

	Country	Persistent HBV Infection	Self Limited HBV Infection
Thursz *et al.* (20) (1995)	Gambia	-	HLA-DRB1*1302
Chen *et al.* (21) (1996)	Caucasians	HLA-B8, A30, DR3, DQA1*0501	-
Thio *et al.* (18) (2003)	Caucasians	HLA-B*08	HLA-A*0301,DRB1*1302
Cotrina *et al.* (28) (1997)	Spain	-	HLA-DRB1*1301 , DRB1*1302
Hohler *et al.* (44) (2005)	Germany	-	HLA-DRB1* 1301, DRB1* 1302
Diepolder *et al.* (29) (1998)	Germany	-	HLA-DR13
Thio *et al.* (22) (1999)	African, American	HLA-DQA1*0501, DQB1*0301	-
Shen *et al.* (24) (1999)	China	HLA-DRB1*10	-
Jiang *et al.* (59) (2003)	China	HLA-DRB1*0301, DQA1*0501, DQB1*0301	HLA-DRB1*1101/1104, DQA1*0301
Meng *et al.* (23) (2003)	China	HLA-DR9 , DQ9	HLA-DRB1*1201
Han *et al.* (25) (2005)	China	HLA-DRB1*06, DRB1*08, DRB1*16	HLA-DRB1*07
Zhang *et al.* (54) (2006)	China	HLA-DRB1*12	HLA-A*02
Xi-Lin *et al.* (60) (2006)	China	-	HLA-DQB1*0503, *0303
Lu *et al.* (61) (2006)	China	HLA-DQA1 * 0302	HLA-DQA1 * 0102HLA-DQA1 * 0301
Yang *et al.* (1) (2007)	China	HLA-DRB1*03, DRB1*07	HLA- DRB1*15
Zhu *et al.* (17) (2007)	China	HLA-DQB1*0502	-
Song *et al.* (62) (2007)	China	HLA-DRB1*0401	-
Liu *et al.* (63) (2007)	China	HLA-DQB1*0201, DQA1*0601, DQB1*0601, DQA1*0201	HLA-DQA1*0102 , DQA1*0104
Singh *et al.* (11) (2007)	China	HLA-DQA1*0501, HLA-DQB1*0301	-
Li *et al.* (64) (2011)	China	HLA-DRB1*07, 12	HLA-B*51,B*15, DRB1*11 , 14
Ahn *et al.* (31) (2000)	Korea	-	HLA-DR6, DR13
Hwang *et al.* (26) (2007)	Korea	HLA-A33, DR7	-
Cho *et al.* (7) (2008)	Korea	HLA-DRB1*0701, DQB1*0301	HLA-DRB1*1302, DQB1* 0609
Karan *et al.* (30) (2002)	Turkey	-	HLA-DR13
Albayrak *et al.*(3) (2011)	Turkey	HLA-B35, CW4, DQ2,DQ8	-
Kummee *et al.* (65) (2007)	Thailand	HLA-DR12	HLA-DR13
Ramezani *et al.* (27) (2009)	Iran	HLA-A*3303	HLA-DRB1*1301
Fletcher *et al.* (66) (2011)	India	HLA-DRB1*0701, B*44	HLA-DRB1*0301

type compared to G/A and A/A genotypes.

Yan *et al.* (53) demonstrated that the -592C allele and the -1082A-819C-592C haplotype in IL-10 gene promoter were associated with an increased susceptibility to acute liver failure in HBV carriers. The study by Zhang *et al.* (54) showed no significant difference in frequencies of genotypes and alleles of IL-10 gene promoter region at position -1082 G/A, -819 T/C, -592 A/C among normal controls, individuals spontaneously recovering from HBV infection, and patients with chronic hepatitis B. However, they reported that frequencies of T/T genotype at position -819 and A/A genotype at position -592 in chronic hepatitis B were significantly higher than that in asymptomatic HBV carriers. Li *et al.* (55) also showed no significant differences in -1082, -819 and -592 of IL-10 gene between cases and healthy controls. An investigation in Iran is also found no significant difference in frequencies of genotypes and haplotypes of IL-10 gene promoter region at position -1082, -819 and -592 among cases with HBV infection and controls but they reported that frequencies of A/A genotype at position -592 and T/T genotype at position -819 were higher in HBV clearance group, while frequency of G/G genotype at position -1082 was higher in persistence group. GCC/GCC and GCC/ACC haplotypes were significantly more frequent in anti-HBe positive patients (56).

4. Conclusions

Hepatitis B virus is the most common cause of acute and chronic liver disease worldwide. Chronic HBV infection is a multifactorial disease which is related to viral genotypes and host genetic factors. Recent studies have shown that HLA and cytokine genetic polymorphisms have an association with the development of chronic HBV infection and the progression of the infection. We

have aimed to review the published literature on polymorphisms of HLA and IL-10 gene promoter associations with HBV infection outcome with the purpose to provide prognostic markers for the outcome of HBV infection.

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Authors' Contribution

Amitis Ramezani: Conception and design of the study (50%), Final approval of the study

(50%). Mohammad Banifazl: Critical revision of the article for important intellectual content. Setareh Mamishi : Revision, Masoomeh Sofian: Critical revision, Ali Eslamifar: Guarantor of integrity of the entire study, Arezoo Aghakhani: Conception and design of the study (50%), Final approval of the study (50%).

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