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TOPIC HIGHLIGHT

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Relationship between cytokine gene polymorphisms and chronic hepatitis B virus infection

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Abstract

Hepatitis B virus (HBV) infection is still a public health problem worldwide, being endemic in some parts of the world. It can lead to serious liver diseases such as chronic hepatitis, cirrhosis, and hepatocellular cancer. The differences in host immune response can be one of the reasons for the various clinical presentations of HBV infection. Polymorphisms of genes encoding the proinflammatory and antiinflammatory cytokines, which are responsible for regulation of the immune response, can affect the clinical presentation of the infection. Particularly, the polymorphisms of the genes encoding cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-10, IL-18, IL-28B, interferon-γ, tumor necrosis factor-α, tumor growth factor-β1, and regulatory molecules like vitamin D receptor and chemokine receptor 5 can be responsible for different clinical presentations of HBV infections. The genomic information about cytokines and other mediators can be important for determining high-risk people for developing chronic hepatitis or hepatocellular cancer and may be used to plan treatment and preventive approaches for these people. In this review, the current knowledge in the literature on the association between cytokine/regulatory molecule gene polymorphisms and clinical course of chronic HBV infection is summarized, and the clinical implementations and future prospects regarding this knowledge are discussed.

Key words: Hepatitis B virus; Cytokine; Polymorphism; Chronic hepatitis

Core tip: The specific polymorphisms of genes encoding cytokines, such as interleukin (IL)-1, IL-8, IL-10, IL-18, IL-28B, tumor necrosis factor-α, interferon-γ, tumor growth factor-β1, and regulatory molecules such as vitamin D receptor and chemokine receptor 5 affect the clinical course of chronic hepatitis B virus (HBV) infection. This review aims to summarize the literature on cytokine gene polymorphisms and chronic HBV infection and discuss future prospects regarding the clinical implication of these polymorphisms.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a serious and common infectious disease of the liver, affecting 240 million people worldwide with an estimated 600000 deaths per year, and remains the major cause for chronic hepatitis, cirrhosis, and hepatocellular carcinoma[1-3]. HBV infection is endemic, particularly in developing countries, and is a serious public health problem[3].

Following acute HBV infection, 1%-5% of adults develop chronic infection[4] (Figure 1). Rate of chronicity is inversely proportional to age, being higher in newborns

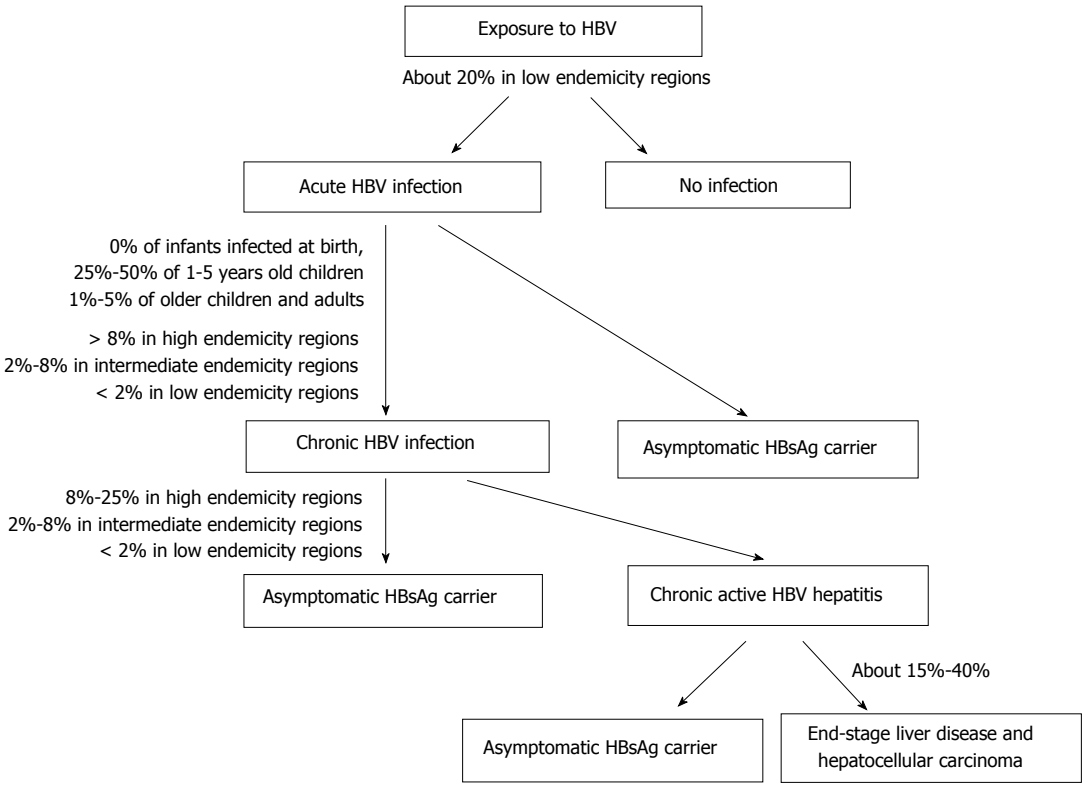

Figure 1 Clinical presentations of hepatitis B virus infections[4,100]. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen.

and children than in adults. The prevalence of chronic HBV infection is also higher (over 8%) in areas where the disease is highly endemic than in those with intermediate and low endemicity[4].

The chronic diseases caused by HBV are chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma[5]. Chronic hepatitis can lead to end-stage liver disease in 15%-40% of patients[6]. A number of factors, including host-related factors (*e.g.*, genetic and immunological background), pathogen-related factors (*e.g.*, viral load, genotype), and environmental factors (*e.g.*, hygiene, nutrition, treatment, vaccination)[7] affect the outcome of HBV infection.

It has been well known that the genetic background of the host and host-pathogen interactions influence the outcome of HBV infection[8-12]. Hepatitis B surface antigen positivity is more common in identical twins than in fraternal twins[13], which indicates that host-related genetic factors have an impact on the course of HBV infection.

Gene polymorphisms such as the single nucleotide polymorphism (SNP; replacement of a nucleotide with another one) may change the structure and biological function of the protein coded by that gene. A SNP in the promoter region of a gene may cause increased or decreased production of the relevant protein. The presence of these types of inherited gene polymorphisms may make a person more susceptible or resistant to a certain disease[14].

Cytokines and regulatory molecules play a fundamental role in the immunopathogenesis of HBV infection. The gene loci for cytokines are defined, and polymorphisms of these genes are suggested to influence the outcome of HBV infection[11]. Therefore, many recent studies have focused on the effect of gene polymorphisms of cytokines on disease outcome and response to vaccination and treatment[10]. Understanding the genetic background of this common public health problem may give rise to new strategies for prevention, treatment, and control of HBV infection.

In this systematic review of the literature, the impact of gene polymorphisms on the course of chronic HBV infection is evaluated and discussed with a focus on polymorphisms of genes encoding cytokines and regulatory proteins.

CYTOKINES

Cytokines represent a large family of molecules, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, IL-18, IL-28, interferon (IFN)-γ, IFN-α, and tumor growth factor-beta (TGF-β). Cytokines play an important role in the initiation and regulation of immune responses and, therefore, might affect susceptibility to HBV and/or the natural course of the infection[9].

In addition to cytokines, antioxidant enzymes (*e.g.*, nitric oxide synthase, manganese superoxide dismutase, glutathione S-transferase), and regulatory proteins (*e.g.*, chemokine receptor 5 (CCR5), vitamin D receptor (VDR), estrogen receptor, mannose binding lectin) may also have a role in the course of HBV infection and polymorphisms of the genes encoding these proteins are evalu-

Table 1 Role of polymorphisms of genes encoding cytokines and some regulatory proteins in chronic hepatitis B virus infection

Cytokine	Allele/ polymorphism	Effect	Ref.
IL-1			
IL-1α			
IL-1β	-511C	Persistent infection	[20-22]
IL-1RN	2	Protective against HBV infection	[18]
IL-6	-174 G/C	No effect	[26]
IL-8	-251AA	Protective against HBV-related cirrhosis	[28]
IL-10	-1082G	Virus clearance, lower HBV viral load, protective against HBV infection	[30,31]
		Persistent HBV infection	[35]
	-592CA	Virus clearance	[35]
		Persistent HBV infection	[36]
	IL-10R K47E	Persistent, chronic infection	[38,99]
IL-18	-148C	Virus clearance	[40]
	+8925G	Virus clearance	[40]
	+13925C	Virus clearance	[40]
	-137C	Protective against HBV	[43,44]
	-607AA	Inhibition of HBV DNA replication	[43,44]
IL-28B		Virus clearance, prevent HBV progression	[46]
		No effect	[51]
TNF-α	-863A	Virus clearance, persistent infection	[68,71,77]
	-238A	Persistent infection	[37,58-62,71]
	-308A	Progressive disease	[55,58,66,77]
		Protective against chronic HBV infection	[76]
	-857CC	Persistent infection	[37,61,62,68]
		Protective against chronic HBV infection	[75]
IFN-γ	+874AA	Viral load, persistent infection	[54]
TGF-β1	-509C	Development of cirrhosis	[80]
	Codon 10T	Development of cirrhosis	[80,83]
		Progression to hepatocellular cancer	[81,82]

HBV: Hepatitis B virus; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; TGF: Tumor growth factor.

ated in various studies[14].

The role of polymorphisms of genes encoding cytokines and some regulatory proteins in chronic HBV infection is summarized below (Table 1).

IL-1

IL-1 is a proinflammatory cytokine with various biological activities[15]. The *IL-1* gene family encodes IL-1α, IL-1β, and their natural inhibitor, IL-1 receptor antagonist (IL-1RN)[15,16]. *IL-1RN* allele 2 polymorphism is associated with an increase in IL-1β production[17], which then increases the production of other cytokines (*e.g.*, IL-2, IL-6, and TNF-α), and stimulates the clearance of HBV[18]. *IL-1RN* polymorphisms, thus, have a protective role against HBV infection[18].

In addition to its proinflammatory action, IL-1β has a role in tumor growth[19]. Polymorphism of *IL-1β* at -511C allele is associated with increased IL-1β level and is a genetic indicator of hepatocellular cancer development in chronic HBV-infected patients[20]. *IL-1β* and *IL-1RN* accessory protein gene polymorphisms are related to chronic and persistent HBV infection[18,21]. Fontanini *et al*[22] reported that *IL-1β* proinflammatory polymorphisms are associated with cirrhosis and end stage liver disease, which are more pronounced in males.

IL-6

IL-6 is an important cytokine that regulates the immune response to HBV infection[15]. IL-6 level is significantly increased in chronic HBV infection[23]. However, studies from Korea and Israel showed that there is no relation between *IL-6* gene polymorphism and chronic HBV infection[24,25]. Similarly, studies from other populations indicate no significant effect of *IL-6* polymorphism at -174G/C on chronic HBV infection[26].

IL-8

IL-8 has been associated with tumors and chronic inflammatory diseases through its mitogenic and angiogenic functions[27]. Qin *et al*[28] indicated that the polymorphism of the *IL-8* gene at -251AA might be protective for HBV-related cirrhosis.

IL-10

IL-10 is secreted mainly from T cells and has an inhibitory action on both inflammatory and immunoproliferative responses. It stimulates the differentiation and proliferation of B cells producing immunglobulin M (IgM), IgG and IgA. Moreover, IL-10 inhibits secretion of various cytokines from T cells and monocytes/macrophages[29]. The polymorphism of *IL-10* at -1082 region that results in increased production of G allele is correlated with virus clearance during intrauterine HBV infection. Moreover, increased IL-10 production has a protective effect against HBV infection[30]. The G/G genotype at -1082 is further associated with lower HBV viral load at the immune inflammatory phase in children with chronic HBV infection[31].

However, there are some conflicting results in the literature evaluating the effect of *IL-10* gene polymorphism on HBV infection. Polymorphisms of genes encoding IL-10 are related to increased hepatocellular cancer risk in Korean, Taiwanese, and Chinese patients[32-34]. A meta-analysis of seven studies by Zhang *et al*[35] indicated that there is an association between the gene polymorphism *IL-10* -1082GA and persistent HBV infection susceptibility. Moreover, this meta-analysis also showed that the gene polymorphism *IL-10* -592CA and the clearance of HBV are associated[35]. The carriers of the -592A allele in the *IL-10* promoter region are proposed to have a higher risk of persistent HBV infection[36]. However, according to some data in the literature, there is no association between *IL-10* gene polymorphisms and chronic HBV infection[37].

IL-10RB is a subunit of receptor complexes for IFN-λ and IL-22, which have antiviral- and hepatocyte-protective activity, respectively. Polymorphism of *IL-*

10RB codon 47 is related to chronic HBV infection in the Korean population[38].

IL-18

IL-18 is a potent proinflammatory cytokine and an immune activator. It is mainly produced in active macrophages and increases induction of IFN-γ and TNF-α, and cytotoxicity of natural killer cells[39].

IL-18 can promote hepatitis B virus clearance. Three polymorphic sites in the *IL-18* gene at alleles -148C, +8925G, and +13925C are associated with HBV clearance in the Korean population[40]. A possible positive relationship between serum IL-18 level and disease severity of HBV infection has been indicated in clinical studies[41]. Three SNPs are defined in the promoter region of the *IL-18* gene that can affect IL-18 production and in return IFN-γ expression[42]. In a study of a Chinese population, the polymorphism at -137 with C allele was associated with protection against HBV infection[43]. Moreover, AA genotype at -607 position causes an inhibition of HBV DNA replication[43]. Migita *et al*[44] studied 204 chronically HBV-infected patients; of these, 43 were inactive HBV carriers and 161 had chronic progressive liver disease including cirrhosis. The authors found that the AA genotype of *IL-18* gene-promoter polymorphisms at position -607 and C allele at position -137 are significantly higher in inactive HBV carriers than in those with chronic progressive liver disease, suggesting that the polymorphisms of the *IL-18* promoter regions (-607 and -137) can be associated with different outcomes of HBV infection[44].

IL-28B

IL-28B, which is also known as IFN-λ-3, is encoded by the *IL-28B* gene. IL-28B inhibits HBV replication in hepatocyte cell lines and has been considered as a potential new treatment for viral hepatitis[45]. The genetic polymorphisms near the *IL-28B* gene are strongly associated with sustained viral response and spontaneous viral clearance in patients with chronic HBV infection. Thus, genetic variation of IL-28B may prevent progression of HBV infection by reducing viral load and liver inflammation[46]. However, some conflicting results have been reported so far. *IFN-λ-3* (*IL-28B*) polymorphism is a reliable predictor of IFN therapy outcome in patients with chronic HBV infection[47]. Moreover, it is a protective factor for HBV infection recurrence and hepatic dysfunction after liver transplantation[48,49]. However, *IFN-λ-3* genotype was reported to have no role in the development of chronic HBV infection among HIV-infected patients[50]. Moreover, a study comparing patients with persistent infection with individuals recovered from HBV infection found that *IL-28B* polymorphism has no association with clearance of HBV and does not influence the outcomes of HBV infection[51].

IFN-γ

IFN-γ has a regulatory role in cellular immunity and functions of cytotoxic T lymphocytes. Antiviral, antiproliferative, immunoregulatory, and proinflammatory actions of IFN-γ play a key role in host defense mechanisms. IFN-γ is secreted from T cells and natural killer cells and regulates T cell response, activating monocytes and macrophages, which then produce an antiviral response by releasing free radicals and proinflammatory cytokines such as TNF-α[52]. The core response element of HBV is sensitive to TNF-α, IFN-γ and IFN-α. Increased levels of TNF-α and IFN-γ intensify the antiviral activity of T lymphocytes[53]. *IFN-γ* gene polymorphism at position +879 causing low IFN-γ level is reported to be higher in patients with chronic HBV infection compared to a control group[25]. Additionally, a negative correlation between necroinflammatory/fibrosis scores and genetic production of IFN-γ and TGF-β1 was reported in HBV-infected patients[25]. A recent study from Turkey revealed that *IFN-γ* gene polymorphism at position +874AA is correlated with viral load and chronic HBV infection[54].

Conde *et al*[55] showed in a recent study performed on 153 patients that higher serum levels of IFN-γ and TGF-β1 are associated with chronic HBV infection, and serum level of IL-10 is lower in patients with active disease[55]. Furthermore, the authors reported that the presence of allele A of the *TNF-α* -308 polymorphism is a risk factor for progressive disease.

TNF-α

TNF-α is a key cytokine that determines host immune response to HBV and viral clearance. Therefore, *TNF-α* gene polymorphism can have a role in the course of HBV infection. TNF-α level and TNF-α receptor expression are increased in HBV-infected patients[56,57]. The *TNF-α* gene is localized at MHC HLA region III and two polymorphisms at -308 G/A and -238 G/A positions of the promoter region may affect TNF-α expression[58,59]. Polymorphisms at these regions may cause an elevation of TNF-α transcriptional activity and increase TNF-α serum level[58]. In HBV-infected German patients, the promoter variant at -238A location is significantly correlated with chronicity of HBV infection[60]. Similarly, a study on Chinese patients showed that polymorphisms at the promoter region at -238GA and -857CC locations are associated with persistence of HBV infection[37,61,62]. Although *TNF-α* polymorphism is not a determinant of HBV clearance in the Italian population, it is suggested to play a role in the prognosis of patients with chronic HBV infection[63]. However, a study performed on Iranian patients reported that *TNF-α* polymorphism has no role in HBV pathogenesis[64]. Similarly, in HBV-infected Japanese patients, there is no association between *TNF-α* polymorphism and progression to hepatocellular carcinoma[65].

A genetic analysis of 956 Chinese Han subjects revealed an association between the polymorphism in the promoter region of *TNF-α* located at -308A and HBV disease progression[66]. A similar result was reported in a study of 27 Turkish patients[67]. *TNF-α* polymorphisms at position -857CC and -863AA are also associated with the development of persistent HBV infection in the Chinese Han population[68]. Another study from the South

Indian population also showed that *TNF-α* promoter polymorphisms (at positions -238A, -308A, -857T, -863A and -1031C) are important host genetic factors that may determine the variable outcome of HBV infection[69].

Cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*) polymorphism may also affect the host immune response, including production of cytokines. Han *et al*[70] reported that *CTLA4* +49GG genotype is associated with lower TNF-α and IFN-γ levels in patients with chronic HBV infection.

Overall results of a meta-analysis involving 19 studies (5245 chronic HBV infection cases and 3181 controls with G238A genotypes) and 11 studies (3576 cases and 2044 controls with C863A genotypes) suggested that there is no significant association between *TNF-α* -238 and *TNF-α* -863 gene promoter polymorphisms and chronic HBV infection[71]. When subgroups were analyzed by ethnicity in this study, no significant association was found in Asian populations, but the *TNF-α* -238A allele is still a risk for chronic HBV infection in European populations[71]. Moreover, carriers of -863A genotype were reported to have increased levels of TNF-α in the liver in response to HBV infection, and this induces hepatocyte damage that may lead to hepatocellular carcinoma[72]. Kao *et al*[73] reported that polymorphism at -863A locus of the promoter region of the *TNF-α* gene is associated with lower TNF-α production and persistence of HBV infection[74]. Furthermore, a meta-analysis including 14 studies (4929 chronic HBV infection cases and 2702 controls with -857 genotype) showed that the *TNF-α* -857T allele reduces the risk of chronic HBV infection in the Asian population[75]. Similarly, it was proposed that the *TNF-α* -308A allele is protective against chronic HBV infection in the Mongolian population[76].

A meta-analysis of 12 studies suggested that polymorphisms -863A and -308G in the *TNF-α* promoter region might be a risk factor for HBV persistence[77]. Since ethnicity plays an important role in HBV infection outcome, conflicting results are reported on the association between *TNF-α* promoter gene polymorphisms and HBV infection outcome.

TGF-β1

TGF-β1 shows an inhibitory effect in the early stages of tumor development, while it stimulates tumor growth, invasion, and metastasis in advanced stages[78]. TGF-β1 plays a critical role in the pathogenesis of liver fibrosis by stimulating extracellular matrix proteins and inhibiting their destruction[79]. Therefore, mechanisms increasing the level of biologically active TGF-β1 have a potential role in the development of liver fibrosis. A study of Chinese patients revealed that even though there is no association between *TGF-β1* -509C polymorphism and cirrhosis, this polymorphism might affect TGF-β1 levels and development of cirrhosis[80]. However, in the very same study, codon 10T polymorphism is related to the development of cirrhosis, but not with progression of disease and plasma TGF-β1 levels[80]. Codon 10T polymorphism in the *TGF-β1* gene was also reported to be associated with progression to hepatocellular cancer[81,82] and cirrhosis[83] in patients with chronic HBV infection.

REGULATORY PROTEINS

Vitamin D

The active metabolite of vitamin D, 1,25-dihydroxyvitamin-D, has immunomodulatory action in addition to its regulatory role in calcium metabolism. It activates monocytes, increases cell-regulated immunity, inhibits lymphocyte proliferation, immunoglobulin, and cytokine synthesis, and inhibits type 1 cytokine secreting T helper (Th1) response while activating Th2 response. Additionally, vitamin D plays a role in programmed cell death. Monocytes, macrophages, and active T lymphocytes carry VDR. While the stimulation of VDR on monocytes and macrophages increases production of TNF-α, IL-1, and prostaglandin E2, stimulation of VDR on lymphocytes inhibits T cell proliferation and production of IFN-γ, IL-2 and TNF-β[84]. Four polymorphisms of the *VDR* gene are associated with various immune diseases[84]. Furthermore, being homozygous for *VDR* gene polymorphism at codon 352 (genotype tt) is significantly less frequent in patients positive for hepatitis B surface antigen, and it was suggested that this genotype provides resistance to chronicity of HBV infection[85]. *VDR* a/a allele is also associated with severity of HBV-related liver disease and with higher viral load[86].

CCR5

An efficient immune response against viral hepatitis should promote inflammatory cells to be activated and to migrate to the liver. Chemokines have important functions during this process by means of their chemotactic and immunoregulatory actions. The CCR5 acts as a receptor for chemokines. Among the chemokines, regulated on activation normal T cell expressed and secreted (RANTES; CCL5), macrophage inhibitory protein-1α (MIP-1α; CCL3), and MIP-1β (CCL4) are natural ligands of CCR5. Both these chemokines and CCR5 regulate T cell functions by mediating polarization, activation, and differentiation of Th1 and cytotoxic T cells[87]. Besides, CCR5 has a regulatory function for the immunoregulatory action of vitamin D.

The frequency of heterozygosity of the *CCR5-delta 32* gene is higher in chronic hepatitis B patients than in controls, which shows the relation of this polymorphism with susceptibility to HBV-related liver disease[86]. *CCR5* 59029A and 59029G alleles are associated with increased chronic HBV infection risk and spontaneous HBV clearance, respectively[88]. The frequency of *CCR5* Wt/mt allele is higher in chronic HBV patients than in healthy subjects, while *CCR5* Wt/Wt allele is more common in patients with severe liver disease than in mild cases[86].

CURRENT INTERESTS AND FUTURE PROSPECTS

Recent gene polymorphism studies have focused on the

clinical implication of polymorphism-HBV infection associations such as gene therapy targets[46], prediction of infection risk, disease progression, chronicity, response to treatment[89] or vaccine[90-94], and susceptibility to mother-to-child transmission of HBV[95].

IL-28B genotyping is suggested to predict the response to pegylated interferon[96] and to provide a valuable gene therapy target due to its reducing effect on HBV viral load and hepatic inflammation[46].

Gene polymorphisms of *IL-1B*, *IL-4*, *IL-4R*, *IL-13*[90,93,94], *IL12A* and *IL12B*[92] are suggested to predict the immune response to HBV vaccination.

Since TNF-α and vitamin D pathways are involved in the susceptibility to, and the outcome of, HBV infection acquired early in life, they can be used clinically to determine the susceptibility to mother-to-child transmission of HBV[95].

Although studies on the clinical application of gene polymorphisms of cytokines have been increasing recently, further clinical studies are needed for widespread use of genotyping in the course of HBV infections.

CONCLUSION

Along with the establishment of the key role of endogenous mediators in the response to infection, effects of host-related factors on the course of chronic HBV infection have been investigated from different perspectives. Some of these studies have focused on the effect of diversity in genes encoding endogenous mediators of inflammatory response to HBV infections.

Inflammatory processes are mostly regulated by proinflammatory and antiinflammatory cytokines, and other mediators, which are determinative for the course of disease. Polymorphisms in genes encoding endogenous mediators may be the underlying cause of clinical differences between patients. Results of the studies summarized in this review suggest that cytokine gene polymorphisms affect the level of cytokines during the inflammatory response to HBV, and thus determine the clinical course of chronic HBV infection. Genomic information with regard to cytokines and other mediators can be used for identifying individuals who are at high risk of developing chronic hepatitis and hepatocellular carcinoma, and for the planning of preventive measures and treatment approaches.

As recent studies have indicated, gene polymorphisms of inflammatory mediators may be important in determining the response to both treatment and vaccine. For example, serum levels of TNF-α in patients who respond to treatment with interferon were found to be higher than those in nonresponders[97]. Granulocyte-macrophage colony-stimulating factor has been reported to increase the response rate to recombinant hepatitis B vaccine[98]. Additionally, genetic factors may play a role in the development of adverse reactions secondary to the vaccine such as arthritis, multiple sclerosis, and other autoimmune diseases. However, further studies are still needed to investigate in detail the effects of genetic polymorphisms and their clinical implications for the response to treatment and vaccine, and development of adverse events.

In conclusion, there is currently a vast amount of evidence on the association between polymorphisms of genes encoding cytokines/regulatory molecules and the clinical course of chronic HBV infection. Conflicting results on the role of specific polymorphisms are probably due to various ethnic groups studied. In the future, determining genetic polymorphisms of mediators that have a role in both the natural course of the infection and the response to treatment and vaccination will contribute significantly to the prevention and treatment of HBV infections by eliminating possible risk factors prior to disease and by development of new treatment approaches.

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