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Review

Impact of host gene polymorphisms on susceptibility to chronic hepatitis B virus infection

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ABSTRACT

Hepatitis B virus (HBV) infection can result in a number of different clinical conditions, including asymptomatic HBV carriers to chronic hepatitis and primary hepatocellular carcinoma. Variations in cytokine genes have been discussed to affect the natural history of HBV infection. These cytokines may involve in the viral binding to the cells, modulating the host immune response to infection and pathological changes in the liver, and affecting the antiviral therapies. Various studies reveal that SNPs play an important role in pathogenesis of HBV. On the other hand, various outcomes of infection cannot be completely shown by genetic factors because these studies have inconsistent results with regard to the possible impacts of host genetic polymorphisms on susceptibility to infection. Therefore, to identify the real effects of host genetic factors in HBV susceptibility and natural history of the disease, studies with large sample size will be needed. In addition, due to the complex interactions of genetic factors it is better to identify synergies of several SNPs. Such studies can provide better insights into the novel methods of diagnosis and treatment. Current review will discuss significant genetic variations in cytokine genes that may affect the susceptibility to the chronic HBV infection.

Contents

Abbreviations: HBV, hepatitis B virus; MHC, major histocompatibility complex; SNP, single nucleotide polymorphism; IFN-γ, interferon gamma; IL-6, interleukin 6; IL-10, interleukin-10; IL-28B, interleukin 28B; TGF-β, Transforming growth factor beta; TNFα, tumor necrosis factor alpha; MIF, macrophage migration inhibitory factor; HLA, human leukocyte antigen.

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1. Introduction

Hepatitis B virus (HBV) is one of the most dangerous pathogens in the world. HBV infection has a dichotomous outcome; it may be acute, or persistent. Chronic hepatitis B virus (HBV) infection is an important infection that leads to major chronic liver diseases such as liver cirrhosis and hepatocellular carcinoma (HCC). Usually, in 5% of HBV infected patients, acute HBV infection can go on to develop chronic infection. This common severe illness is the reason of high mortality in the year worldwide (more than one million deaths). It is estimated that there are more than 200 millions people with chronic HBV infection in the world and 75% of them are from Asia. It is estimated that more than 25% of chronic HBV infected patients in Asia will die because of the HBV related chronic diseases. Chronic HBV infection is a major public health problem and an endemic disease in developing countries (Lavanchy, 2004).

Transmission routes of hepatitis B are different in various parts of the world. In areas with high prevalence, HBV is transmitted mainly from mother to infant at birth via vertical transmission. The rate of vertical transmission is more than 90%. The most important route of transmission in areas with medium prevalence is transmission from an infected person during childhood and adolescence by horizontal transmission. In regions with low prevalence, unsafe sexual contact and injecting the drug with unsterilized needles are the most important routes of transmission in adults. Hepatitis B virus can survive outside of the body for a long time. Therefore, exposure to contaminated things such as toothbrushes, razors, toys and body fluids can increase the risk of HBV infection. Blood transfusion and contact with infected blood are also important ways in HBV transmission. The chance of infection transmission through the blood and blood products is about 6 to 8%. The outcomes of HBV infection vary among different infected subjects and not yet completely known. HBV can lead to different clinical manifestations and/ or no infection (Iino, 2002; Rantala and Van de Laar, 2008; Schweitzer et al., 2015).

It seems there are three factors which can determine different natural history of HBV infection in infected subjects (Abel and Dessein, 1997; Ferrari, 1995; Guidotti and Chisari, 2001; McNicholl, 1998; McNicholl and Cuenco, 1999; Thursz, 2000). First of all is virological factors such as viral load, genotype and genetic variability in HBV virus genome. These pathogen-related factors can affect the host immune responses. The second is environmental factors such as immunological factors, treatment and nutrition. These parameters can change the outcome of HBV infection and host susceptibility to HBV infection. Finally, it is believed that the host genetic factors are the third agent which can change the outcomes of HBV infection. Although the effects of virological and environmental factors on HBV infection have been well known but the influence of the host genetic factors on susceptibility to HBV infection is not clearly understood (Dean et al., 2002; Grünhage and Nattermann, 2010; Hill, 1998a; Hill, 1998b; Mackay, 2006; McNicholl et al., 2000; Thursz, 1997; Thursz et al., 2011). Studies on identical twins reveals that host genetic factors can alter the natural history of HBV infection (Lin et al., 1989). The major histocompatibility complex (MHC) class I and class II, vitamin D receptor, cytokine, chemokine and their receptor genes are important compounds which have been studied for the relationship between the polymorphisms such as single nucleotide polymorphism (SNP) and the susceptibility to HBV infection. These polymorphisms, especially those one in the promoter region of genes, can affect the function and levels of the proteins. These events can increase or reduce the susceptibility to infectious diseases (de Andrade, 2004). Therefore, the focus of current article is to review the relationship between human genetic alleles and susceptibility to HBV infection.

2. Genetic factors affecting the susceptibility to HBV infection

2.1. Cytokines

Cytokines are small proteins (approximately 5–20 kDa) that have important roles in cell signaling. They are produced by various cells such as macrophages, lymphocytes, mast cells, endothelial cells, fibroblasts, and stromal cells. Cytokines regulate host immune responses against infection, inflammation, trauma and cancer through their receptors (Dinarello, 2007).

Type 1 cytokines such as interleukin-2 (IL-2), interleukin-12 (IL-12), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) are produced by helper T 1 (Th1) lymphocytes and enhance cellular immune responses. On the other side, type 2 cytokines such as Transforming growth factor beta (TGF-β), interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13) and interleukin-28 (IL-28) are produced by T helper 2 (Th2) lymphocytes and regulate humoral immune responses. Some cytokines are cross-regulatory factors, it means that IFN-γ can decrease the levels of type 2 cytokines while IL-10 can decrease the levels of type 1 cytokines (Daniel et al., 1996).

Inflammatory cytokines are induced by oxidative stress. Some cytokines can control the release of other cytokines. This event leads to increased oxidative stress in chronic inflammations (Chokkalingam et al., 2013; David et al., 2007; Vlahopoulos et al., 1999).

A number of cytokines have been associated with chronic hepatitis B infection (Table 1.). Some of them have polymorphisms in their genes which have influenced the susceptibility to other chronic inflammations such as periodontal diseases (Heidari, 2014; Heidari et al., 2015a; Heidari et al., 2014a; Heidari et al., 2013; Heidari et al., 2015b; Heidari et al., 2014b; Sanchooli et al., 2012; Solhjoo et al., 2014). A number of cytokines such as IL-28 (Heidari et al., 2016), IL10 (Moudi et al., 2016) have changed natural history of HBV infection. Although, the key role of these T cell derived compounds in the pathogenesis of hepatitis B infection is unknown (McNicholl et al., 2000; Thursz, 1997). The relationship between chronic HBV infection and polymorphisms of genes encoding more important cytokines is reviewed in the following.

2.1.1. IL-6

Interleukin 6 (IL-6) is a pro-inflammatory and anti-inflammatory cytokine. IL-6 is secreted by T cells and macrophages after tissue damages leading to inflammation and is responsible for fever in infectious diseases, either acute or chronic. IL-6 can also improve osteoclast differentiation and bone absorptive process (Sanchooli et al., 2012; Scheller et al., 2011).

It is involved in the pathogenesis of HBV infection and HBV-related clinical progression (Palumbo et al., 2015). During infection, T cells and macrophages produce IL-6 to regulate immune responses (Scheller et al., 2011).

IL-6 cytokine stimulates the immune responses against hepatitis B virus infection. It seems that the level of IL-6 expression is associated to the susceptibility to chronic HBV infection (Dinarello, 1996; Song et al., 2000). It can regulate the biological function of several cells, such as hepatocytes. Increased levels of IL-6 have been reported in patients with chronic HBV, cirrhosis and HCC. It has been found that hepatitis B virus replication could be suppressed by IL-6, which leads to reduced the accumulation of HBV covalently closed circular DNA (cccDNA) in hepatocytes (Kuo et al., 2009; Palumbo et al., 2015). In addition, HBV infection is largely recognized by liver macrophages such as Kupffer cells. Induced Kupffer cells activate the nuclear factor kappa B (NF-kappaB) and secret IL-6 cytokine. Subsequently, IL-6 affect HBV gene expression and replication in hepatocytes (Hösel et al., 2009). Thus, it is suggested that IL-6 can be a diagnostic marker of chronic HBV infection.

The IL-6 is encoded by the IL-6 gene localized on chromosome 7p21. Some studies demonstrated that polymorphisms of this gene can affect the concentration of IL-6 in serum (Erciyas et al., 2010; Mesa et al., 2014). Polymorphisms in promoter region of IL-6 gene affect transcription and expression of IL-6 in individuals. There are three SNPs in the *IL-6* promoter region (*−597G/A*, *−572C/G* and *−174G/C*), that have been reported in chronic HBV patients. These SNPs control the up-regulation of IL-6 levels. However, studies conducted by Ben-Ari et al. (2003), Park et al. (2003) and Giannitrapani et al. (2013) have been reported no