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Review

Current concepts on immunopathogenesis of hepatitis B virus infection

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ABSTRACT

Hepatitis B virus (HBV) infection is a leading cause of liver damage and hepatic inflammation. Upon infection, effective antiviral responses by CD8+ T cells, CD4+ T cells, Natural killer (NK) cells, and monocytes can lead to partial or complete eradication of the viral infection. To date, many studies have shown that the production of inhibitory cytokines such as Interleukin 10 (IL-10), Transforming growth factor beta (TGF-β), along with dysfunction of the dendritic cells (DCs), and the absence of efficient innate immune responses could lead to T cell exhaustion, development of persistent infection, and inability to eradicate the viral infection from liver. Understanding the immunopathogenesis of the virus could be useful in providing further insights toward novel strategies in the eradication of HBV infection.

1. Introduction

Infection with hepatitis B virus (HBV) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Current vaccine and antiviral drugs make this infection preventable. However, despite considerable therapeutic advancements, worldwide, HBV infection is still the third leading cause of death due to liver cancer. In addition, overcoming persistent HBV infection remains a great challenge. HBV does not directly damage the hepatocytes. However, by integrating its genome into the host chromosomal DNA and owing to interactions between the virus and the immune system, the persistence of infection and liver damage is accelerated. Activation of the immune responses against viral infections is associated with both liver damage and virus elimination. However, viruses use several mechanisms to debilitate the immune responses (Terrault et al., 2016; Gerald Mandell and Mandell, 2010).

2. HBV virology

2.1. Epidemiology

Worldwide, it is estimated that two billion people are infected with HBV and about 240 million people are chronically infected. It is also generally known that almost half of the World's population live in areas with high prevalence of HBV infection. The World Health Organization (WHO) reported that annually, about 650,000 people die from complications of chronic HBV infection. Alone, HBV is responsible for about 45% of cases of hepatocellular carcinoma (HCC), and about 30% of cirrhosis cases, especially in low income countries (Terrault et al., 2016; Schweitzer et al., 2015).

In many countries, newborns or children are vaccinated. Although this strategy has been effective in reducing the prevalence of infection in most regions around the world over the past decade, it has not had a significant effect on reducing the cases of HCC. Frequent use of non-sterile needles and syringes and unprotected sexual contact plays important roles in the transmission of infection. Infected mothers, especially those who are HBsAg-positive with high viremia, transmit the viral infection to the fetus congenitally. Transmission of infection to infants is very high in the second and third trimesters of pregnancy, in the perinatal period and especially, among infected mothers who are not under prophylaxis (Gerald Mandell and Mandell, 2010; WHO, 2015; Papastergiou et al., 2015).

In areas where the prevalence of infection is high, such as in Asia, infections are mainly transmitted maternally and are chronic. However, in areas where the prevalence of infection is comparatively low, such as in Europe, the major route of transmission is through unsafe sexual contact and injections such as among drug abusers (WHO, 2015).

The transmission modes of hepatitis C virus (HCV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis D

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virus (HDV) are identical, and concurrent infections lead to severe complications and increase the risk of liver cirrhosis, HCC and death. As and example, among patients with HBV-HIV co-infection, effective responses to general medication is relatively lower and the mortality rate is higher compared to cases of patients who are infected with HBV only. Other complications which could occur during co-infection are increased risk of cross-resistance, liver damage, and increased levels of alanine transaminase (ALT), and the development of fulminant hepatitis (WHO, 2015).

Since the risk of HBV infection among patients with HIV infection is very high, they should be screened for HBsAg and anti-HBs antibody, and in the absence of effective immune responses, the efficient vaccine should

be prescribed. Nevertheless, the response to HBV vaccination in patients with HIV infection and those with low levels of CD4 + T cells is very low in comparison with HIV-negative patients. According to the WHO recommendations, four double (40 μg) doses of HBV vaccine should be administered to patients with HIV infection instead of the regular schedule (three 20 μg dose) (WHO, 2015; Vos et al., 2016).

2.2. HBV genotypes

Currently, 10 genotypes (A-J), and at least 35 subgenotypes of HBV has been reported worldwide. Spontaneous errors of HBV reverse transcriptase enzyme is responsible for these genetic variations (Ott et al., 2012; Sunbul, 2014).

Based on antibody responses to the HBs antigen, HBV is categorized into several serotypes; four major serotypes (adw, adr, ayw, ayr), and 9 minor serotypes have been identified. These serotypes and genotypes are different in properties, including geographical distribution, disease severity, treatment response, risk of developing HCC and resistance to HBeAg seroconversion. The highest probability for developing HCC is observed among genotypes C and F and some subtypes of genotype A. Genotype A is an independent risk factor for the progression of the acute to the chronic form of the infection. The acute infection occurs more frequently among cases of infection with genotypes A and D compared to genotypes B and C. All acute forms of infections could lead to chronic infections (Mohd Hanafiah et al., 2013; Fields et al., 2007).

Spontaneous HBeAg seroconversion in genotype C and D is less frequent compared to genotypes A and B. Deadly liver complications, including cirrhosis and HCC are associated with a higher extent to genotypes C and D compared to other genotypes. Response to Interferon therapy, especially among cases of infection with genotypes A and B is higher compared to that of genotypes C and D. Spontaneous HBeAg seroconversion occurs more frequently among patients with genotype B compared to patients infected with genotype C. Recent studies have shown that mutations in Pre-core (pre-C) of HBV genome is the most frequent mutation that occurs in HBV and has associations with clinical complications. Such mutations are more likely to occur in genotype C compared to genotype B (Gerald Mandell and Mandell, 2010; WHO, 2015; Dancygier, 2009).

Basal core promoter (B CP) is located between nucleotides 1744–1804. It controls the transcription of the pre-core and core genes. Various types of mutations in this gene have been reported as follows:

1) Stop codon mutation at position 1896 which leads to inability in expressing HBeAg.
2) Mutations at positions 1762 and 1764 which leads to reduced production of HBeAg and increased host immune responses. These mutations leads to the occurrence of HBeAg-negative form of chronic hepatitis B (CHB). Also, mutations in the pre-core genes are associated with increased pathogenicity. Preliminary studies have shown that pre-core mutants may be related to severe chronic liver and acute liver failures (Hunt et al., 2000).

Furthermore, pre-core and/or BCP mutants in conjunction are associated with reduced responses to treatment with Pegylated interferon-α (PEG-INF-α), Double mutations in the BCP region at nucleotides 1762 and 1764 are associated with severe liver disease, fulminant hepatitis, cirrhosis and HCC (Sonneveld et al., 2012; Takahashi et al., 1995; Baumert et al., 1996; Fang et al., 2002; Kao et al., 2003).

3. HBV infection

HBV infection can be self-limiting or chronic. While 95% of infected adults are capable of spontaneously clearing the viral infection within six months, 30–90% of infected children between years one to five cannot clear the infection during their lifetime and are more likely to become chronic patients. The frequency of adults who develop chronic form of the infection is about 2–6% that is noticeably lower compared to children. The risk of death from cirrhosis and HCC in patients with chronic hepatitis is about 15–25% (Gerald Mandell and Mandell, 2010; WHO, 2015; Prevention CfDCa, 2015).

3.1. Acute infection

More than 95% of immune-competent people with acute hepatitis clear the viral infection effectively; treatment should only be given to those with extreme acute and fulminant hepatitis infection. Acute infection is usually self-limited with consequence of inflammation and necrosis of hepatocytes. The mortality rate in acute infection is around 0.5–1% (Gerald Mandell and Mandell, 2010; Kasper and Fauci, 2013).

3.2. Chronic hepatitis

The main serological biomarker of chronic hepatitis is the presence of HbsAg in blood or serum for more than six months. The spectrum of disease varies in patients with chronic infection. In most cases, the infection is asymptomatic without any intense liver damage. However, in some cases, it leads to fibrosis, cirrhosis, and increased risk of HCC. These effects could occur many years after the establishment of the primary infection. Long-term studies on patients with chronic infections indicates that the probability of development of primary infection to cirrhosis within five years of onset of the disease is about 8–20%, while the incidence rate of liver failure and hepatocellular carcinoma is around 20%, and < 1–5%, respectively. Several significant risk factors such as co-infection with HIV, HCV and hepatitis D virus (HDV) and other factors such as alcohol abuse are responsible for the progression of chronic infection to cirrhosis, HCC and ultimately death (Gerald Mandell and Mandell, 2010; WHO, 2015; Kasper and Fauci, 2013).

According to the WHO guidelines, chronic infection itself is categorized into several phases, including “immune-tolerant”, “immune-active”, “immune-control”, “immune-escape” and “Reactivation”(WHO, 2015).

3.2.1. Immune-tolerant

Immune-tolerant phase is mostly observed in children and young adults. Most of them remain HBsAg-positive usually 10–30 years after the initial infection in the perinatal or infancy age. In this group of patients, serum HBV DNA levels are high (usually more than 200 000 IU/mL) and alanine aminotransferase (ALT) levels may be normal or slightly increased. HBeAg is detectable in serum and can be cleared spontaneously in some cases, and liver inflammation and progression to fibrosis is very low (WHO, 2015; Dancygier, 2009; Rubin et al., 2008).

3.2.2. Immune-active phase

In this phase, HBeAg and anti-HBe antibody are detectable and liver inflammation can occur. Serum ALT levels may be abnormal or fluctuate and usually is associated with declines in virus replication (HBV DNA levels > 2000 IU/mL). Liver damage and fibrosis may be present and can be severe. This phase can take a few weeks to several years with