

Immune mechanisms in chronic viral hepatitis

Kronik viral hepatitin immun mekanizmaları

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ABSTRACT

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are the major causes of chronic liver inflammation worldwide. Although both viruses induce immune-mediated acute and chronic inflammatory liver diseases, the natural history and outcome of HBV and HCV infections are different. This is because of both viruses and host features, like genetic, immunologic and environmental. Hereby, we present the immune mechanisms and immunopathogenesis involved in chronic viral hepatitis.

Keywords: HBV, HCV, Innate immunity, Adaptive immunity

ÖZ

Hepatit B ve Hepatit C virüsleri tüm dünyada kronik karaciğer inflamasyonuna neden olan başlıca nedenlerdir. Bu iki virus de her ne kadar immune aracılıklı akut ve kronik inflamatuvar karaciğer hastalıklarına neden olsa da HBV ve HCV enfeksiyonlarının seyri farklıdır. Bunun nedeni, her iki virüsün ve konakçıların genetik, immünolojik ve çevresel özelliklerine dayanmaktadır. Biz bu yazımızda, kronik viral hepatitlerin immün mekanizmalarından bahsedeceğiz.

Anahtar kelimeler: HBV, HCV, Doğuştan bağışıklık, Edinilmiş bağışıklık,

Introduction

The viruses and the host's defense system are often in a race in the early stage of viral infections. The initial defense is the body surface and once it was breached, early 'non-specific' or innate immune defenses such as interferon (IFN), natural killer (NK) cells, and macrophages become activated so that, different cell types contribute to eliminate the viral infections in liver, like CD8+ T cells, liver dendritic cells, Treg cells etc.

The host immune response has several roles in viral hepatitis, it contributes viral control, clinical recovery and protective immunity but on the other hand it may cause chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Chronic liver diseases develop frequently by hepatitis B viruses (HBV) and hepatitis C viruses (HCV) which induce acute and chronic liver disease by different routes of interacting to the host immune system. In hepatic parenchyma, besides hepatocytes, hepatic microenvironment and the particular liver sinusoidal cell populations also modulate hepatic immune responses together. Infections of hepatitis B and C viruses mostly trigger adaptive immune responses and clearances may happen in acute phases.

Hepatitis B Virus

Hepatitis B virus is an important cause of chronic liver inflammation worldwide. Most of the chronically infected patients remain largely asymptomatic without life-threatening liver disease however 10-30% of the patients develop chronic liver disease which may progress to liver cirrhosis or liver cancer [1]. The rate of HBV chronicity is low in adult infections (5% or lower) but age and route of infection may influence the outcome of exposure such as infections in neonatal life lead to high rate of HBV persistence [1, 2]. In a typical case of acute infection with

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hepatitis B, HBV DNA is detectable in the circulation (by PCR) within 1 month of infection, but it remains relatively low levels of 10^2 – 10^4 copy/ml for up to 6 weeks before secreted HBeAg and HBsAg increase to their peak titers. HBV core antigen (HBcAg) specific IgM appears early in acute phase followed by HBcAg-specific IgG persists for life irrespective of the outcome of infection. Approximately 10–15 weeks after infection, serum alanine aminotransferase (ALT) levels begin to rise which indicates T-cell-mediated liver injury. However, most of the HBV DNA in the serum and the liver can be cleared before the ALT peak, as shown in experimentally infected chimpanzees [3]. Production of antibodies directed against envelope antigens which is associated with the clearance of circulating virus particles in acute HBV infection by the strong polyclonal, multispecific CD4⁺ T cell responses to nucleocapsid antigens, CD8⁺ T cell responses to envelope nucleocapsid and polymerase antigens are found in patients who finally clear acute infection. However, in chronic infection only weak T cell responses can be elicited which indicates that immune escape has been developed [4].

Innate immune responses

Most of the HBV DNA can be cleared from the serum and the livers of experimentally infected chimpanzees before a detectable adaptive immune response occurs in the liver [3]. Antiviral effects of IFN- α and IFN- γ (type I IFNs) have been shown in transgenic mice models which have chromosomal replication-competent copies of HBV genomes in their hepatocytes [5]. In this model IFN- α and IFN- γ induced mechanisms inhibit the formation of new HBV capsids, also destabilize existing capsids and degrade pre-formed HBV RNA [5, 6] whereas this antiviral effect seems to be proteasome dependent [7]. In addition, in this model, down regulation of HBV replication can also be mediated by IFN- γ that is produced by activated natural killer T (NKT) cells [8, 9] and T cells [10]. Recently, it was shown that low levels of IFN- α and selected ISGs are transiently induced in HBV-infected primary human hepatocytes and modest IFN- α elevation is also observed after transfection of a human hepatoma cell line with a region of pregenomic HBV RNA that is required for viral replication [11].

Adaptive immune responses

Adaptive immune responses such as HBV-specific CD8⁺ T cell responses play a key role in viral clearance and disease pathogenesis. So that, failure of priming, expanding or

differentiation of effector memory T cell response to HBV and/or effective evasion of this response could be responsible for viral persistence [10, 11]. Naïve or antigen experienced HBV-specific T cells could also become anergic or exhausted as a result of activation of additional negative regulatory pathways involving cytotoxic T-lymphocyte antigen-4 (CTLA-4), T-cell immunoglobulin, mucin 3 (Tim-3) [12, 13], antigen overload and excessive T cell stimulation [14], action of regulatory T cells [15], and relative intrahepatic abundance of selected cytokines (e.g. IL-10 or TGF- β) or enzymes (e.g. arginase) with immunosuppressive potential [16, 17]. As a result, it can be concluded that primary and secondary lack of immunological responses to HBV contributes to the establishment of persistent HBV infection.

Hepatitis C Virus

Hepatitis C Virus is another cause of chronic liver inflammation worldwide which has the chronicity rate of 70-80% of the infected HCV patients, whereas 15-25 % of the patients may develop liver cirrhosis [18]. Although development of a protective vaccine is essential, development of HCV vaccine is not easy due to the genetically high diversity in which there are seven major genotypes with 30-35% diversity and over 60 subtypes [19]. HCV bind and entry into the host cell with a multistep process involving HCV envelope glycoproteins E1 and E2 together with several attachment and entry factors such as CD81, scavenger receptor class B type I, members of the claudin family and occludin [20, 21]. Resolved acute HCV infected patients exhibit vigorous polyclonal, multispecific CD4⁺ T cell responses and these T cells exhibit a Th1 phenotype [22-24]. Immunodominance of an NS3 epitope has also been reported [25, 26]. However, in chronic HCV infection CD4⁺ T cell responses are less strong and are directed at fewer epitopes. These cells exhibit a Th2 phenotype and no immunodominant CTL epitopes have been identified [27-28]. There are also lots of studies trying to improve a successful vaccine [29].

Innate immune responses

HCV induces type I IFN production in infected cells by contact with TLR3 in the endosomal compartments, or by recognition of the polyuridine motif of the HCV 3' untranslated region (UTR) with the retinoid acid-inducible gene I (RIG-I) in cytoplasm [30]. Secreted IFN- α induces an anti-viral condition that extend to non-infected neighboring cells. This process activate JACK/STAT pathway, that induce IFN-stimulated genes (ISGs) which degrades viral

and cellular RNA [30]. Type I IFNs are also produced by non-parenchymal cells, particularly by plasmacytoid DCs (pDC) in inflamed tissues and draining lymphoid nodes [31]. HCV may attenuate IFN- production by hepatocytes, by a mechanism which requires infection, and pDCs, by direct interaction independent of infection [30]. NK cell responsiveness was shown in a large immunogenetic study in which the presence of individual killer cell Ig-like receptor/HLA (KIR/HLA) compound genotypes correlates with HCV clearance [32]. Inhibitory receptors (KIRs) and cytokines (that attenuate the adaptive immune response, such as TGF- and IL-10) production overexpression of NK cells from HCV-infected patients according to healthy controls was also reported, in vitro [33]. In addition, there is an increasing role for microRNAs in mediating HCV innate immune evasion strategies, including miR-122 and miR-21 [34, 35].

Adaptive immune responses

Nearly after 8-12 weeks of HCV infection, adaptive immune responses occur and if precisely directed CD4+ T cell responses are detected in acutely infected patients who later develop chronic hepatitis. These T cells undergo rapid exhaustion with sequential loss of IL-2 production, proliferation and IFN- production. Additionally, increased expression of the inhibitory receptors of T cell immunoglobulin domain and mucin domain 3 (TIM-3), programmed death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are found [36]. Functionally impaired virus specific CD8+T cells are also unable to secrete antiviral cytokines, such as IFN-. By these cells, weak and dysfunctional HCV-specific CD4+ T cell responses are seen in chronically HCV-infected patients. Also, a higher frequency of suppressive CD4+CD25+ T cells has been found in these patients [37]. Some studies indicate that HCV-specific protective immunity can occur in at least some recovered patients, its incidence and duration need to be further studied [38,39].

Key Points

- Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are the major causes of chronic liver inflammation worldwide.
- Although both viruses induce immune-mediated acute and chronic inflammatory liver diseases, the natural history and outcome of HBV and HCV infections are different.
- The difference is because of both viruses and host

features, like genetic, immunologic and environmental factors.

- Here, we present chronic viral hepatitis immune mechanisms.

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