Review

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Therapeutic vaccines and immune-based therapies for the treatment of chronic hepatitis B: Perspectives and challenges

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The treatment of chronic hepatitis B virus (HBV) infection has greatly improved over the last 10 years, but alternative treatments are still needed. Therapeutic vaccination is a promising new strategy for controlling chronic infection. However, this approach has not been as successful as initially anticipated for chronic hepatitis B. General impairment of the immune responses generated during persistent HBV infection, with exhausted T cells not responding correctly to therapeutic vaccination, is probably responsible for the poor clinical responses observed to date. Intensive research efforts are now focusing on increasing the efficacy of therapeutic vaccination without causing liver disease. Here we describe new approaches to use with therapeutic vaccination, in order to overcome the inhibitory mechanisms impairing immune responses. We also describe innovative strategies for generating functional immune responses and inducing sustained control of this persistent infection.

Introduction

Worldwide, two billion people have been infected with the hepatitis B virus (HBV) at some time, more than 370 million currently have chronic HBV infection, and about one million die each year from HBV-related liver diseases. HBV is a non-cytopathic virus, and the host immune response determines whether the virus is cleared or whether immunopathy and liver damage are induced. Persistent inflammation during chronic HBV infection results in liver cirrhosis or hepatocellular carcinoma in 25% of patients. HBV is currently the second leading carcinogen after tobacco, with up to 80% of hepatocellular carcinoma cases worldwide attributable to HBV [1]. Individuals with chronic HBV infection also serve as the primary reservoir for viral spread. Preventive vaccination is the most effective way to reduce the global incidence of hepatitis. Efficient vaccines against hepatitis B have been available for over 20 years, and their use should decrease the incidence of HBV infection [2]. By contrast, the treatment of chronic HBV infection is based on the use of antiviral agents. These agents have improved considerably over the last 10 years, with the development of molecules targeting the HBV polymerase and decreasing viral replication. The major goals of anti-HBV treatment are to prevent the development of progressive disease, specifically cirrhosis, liver failure, and hepatocellular carcinoma. However, although currently available antiviral drugs efficiently decrease serum viral load to undetectable levels, they fail to eradicate infection due to the persistence of HBV covalently closed circular DNA (cccDNA) in hepatocytes and the emergence of resistant viruses [3,4]. In addition, such drugs rarely result in the long-term immunological control of HBV infection through the elimination of residual infected hepatocytes, hepatitis B "e" antigen (HBeAg) seroconversion and/or hepatitis B surface antigen (HBsAg) clearance. Moreover, long-term treatment is expensive and may result in problems of toxicity and intolerance.

Both the adaptive and innate immune responses are known to be involved in viral clearance during HBV infection [5]. There is a clear dichotomy in the profile of the immune responses observed, depending on whether patients naturally resolve viral infection or develop chronic infection. Patients with self-limited acute hepatitis B display multi-specific CD4 and CD8 T-cell responses, with the secretion of antiviral cytokines and the production of anti-HBV antibodies. By contrast, patients suffering from chronic infection have very weak or functionally impaired immune responses. Therapeutic vaccination has been proposed as a potentially promising strategy for controlling viral infection, based on these observations. Therapeutic vaccination aims to eliminate persistent viral infection, by stimulating the patient's immune responses.

In this review, we first outline the characteristics of cell-mediated immune responses and the immunosuppressive environment generated during chronic HBV infection. We then

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Abbreviations: HBV, hepatitis B virus; cccDNA, covalently closed circular DNA; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; NK, natural killer; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; DCs, dendritic cells; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte antigen 4; Bim, Bcl2-interacting mediator of cell death; Tregs, regulatory T cells; mDCs, myeloid DCs; pDCs, plasmacytoid DCs; IC, immune complexes; HBcAg, hepatitis B core antigen; Th1, T helper 1; PBMCs, peripheral blood mononuclear cells; CIK, cytokine-induced killer; TCR, T-cell receptor; ALT, alanine amino-transferase.

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describe current and future approaches for manipulation of the immune system to achieve sustained control of this persistent infection.

How is host immunity altered during chronic HBV infection?

The immune response to viral infection is orchestrated in several stages, which function together to eliminate the pathogen and leave the host with memory cells for defense against subsequent infections. During the early phases of acute HBV infection, natural killer (NK) cells are the first line of host defense, and the activation of these cells helps to reduce viral load, through the secretion of interferon (IFN)-γ [6]. However, the activation of these cells is rapidly checked and this is temporally associated with a surge in interleukin (IL)-10 at the time of peak viremia [7]. Adaptive immunity is then induced by 5–6 weeks post-infection, the CD8 and CD4 T-cell populations expand and become major contributors to viral control. HBV-specific T-cell responses participate in the elimination of infected hepatocytes, initially through antiviral cytokine secretion (IFN-γ and tumor necrosis factor (TNF)-α) and then through the production of cytotoxic molecules, once the level of MHC-class I peptide complexes on infected cells has decreased [8–10]. The complete control and eradication of infection are achieved by humoral responses, in which circulating viral particles are neutralized by protective anti-HBs antibodies.

The functional impairment of immune responses is a key feature of chronic HBV infection (Fig. 1) [11]. When T cells encounter HBV antigens presented by intrahepatic antigen-presenting cells, such as liver-resident dendritic cells (DCs), Kupffer cells, or liver sinusoidal endothelial cells, the co-stimulation signals received by T cells are too weak, driving the immune response toward tolerance rather than functional activation. The IFN-α and IL-8 cytokines produced by hepatocytes and inflammatory cells in liver promote NK cell-mediated hepatocyte death and liver damage [12]. T-cell defects are directly related to the sustained exposure of these cells to viral antigens, such as HBsAg and HBeAg, which are produced in large amounts over a period of decades during chronic infection. This chronic exposure to antigens leads to the progressive exhaustion of T cells, which lose their effector functions, such as cytokine production (TNF-α and IL-2), cytotoxicity, and proliferation. Two major inhibitory receptors at the cell surface, programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4), have been identified as regulators of CD8 and CD4 T-cell effector function [13,14]. PD-1 is over expressed on HBV-specific T cells, and its level of expression is correlated with viral load [15]. PD-1-over expressing T cells produce only small amounts of IFN-γ and cannot differentiate into memory cells [16]. Ultimately, the HBV-specific T-cell population may be entirely deleted following prolonged exposure to high doses of HBV antigens. For example, CD8 T cells specific for dominant epitopes have been shown to be undetectable in the liver and peripheral blood of patients with HBV viral loads exceeding 10^7 copies/ml [17]. It has also recently been shown that pro-apoptotic genes are more strongly expressed in HBV-specific CD8 T cells from patients with chronic infection than in those

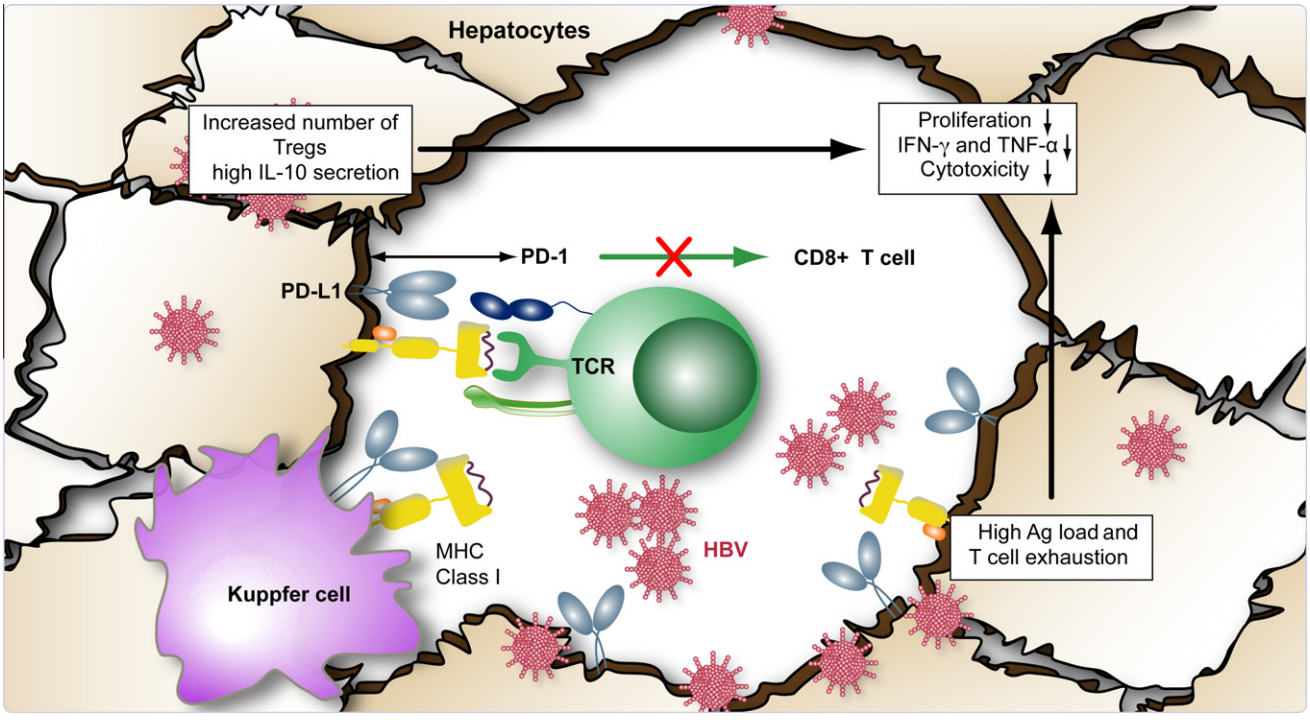

Fig. 1. Impairment of T-cell responses in chronic hepatitis B. T cells circulate in the liver through the sinusoidal network, in which they come into contact with hepatocytes and antigen-presenting cells (Kupffer cells and liver sinusoidal endothelial cells). During chronic hepatitis B virus infection, CD8 T cells in the liver encounter virus particles, viral antigens, and infected hepatocytes. They interact with infected hepatocytes and Kupffer cells through the T-cell receptor (TCR)-MHC class I-peptide complex. Hepatocytes over-expressing PD-L1 during chronic infection provide CD8 T cells with an inhibitory signal via the PD-1 pathway. This negative signal results in the impairment of T-cell functions: decreases in proliferation, cytotoxic function and in the production of anti-viral cytokines (IFN-γ and TNF-α). The presence of a large number of regulatory T cells (Tregs) and high levels of IL-10 secretion also contribute to T-cell exhaustion.