ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 March 7; 28(9): 881-975

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 28 Number 9 March 7, 2022

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The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
March 7, 2022

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World J Gastroenterol 2022 March 7; 28(9): 881-896

DOI: 10.3748/wjg.v28.i9.881

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Innate and adaptive immune escape mechanisms of hepatitis B virus

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Tai DI

Received: February 4, 2021
Peer-review started: February 4, 2021
First decision: July 27, 2021
Revised: August 9, 2021
Accepted: January 29, 2022
Article in press: January 29, 2022
Published online: March 7, 2022

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Abstract

Chronic hepatitis B virus (HBV) infection is an international health problem with extremely high mortality and morbidity rates. Although current clinical chronic hepatitis B (CHB) treatment strategies can partly inhibit and eliminate HBV, viral breakthrough may result due to non-adherence to treatment, the emergence of viral resistance, and a long treatment cycle. Persistent CHB infection arises as a consequence of complex interactions between the virus and the host innate and adaptive immune systems. Therefore, understanding the immune escape mechanisms involved in persistent HBV infection is important for designing novel CHB treatment strategies to clear HBV and achieve long-lasting immune control. This review details the immunological and biological characteristics and escape mechanisms of HBV and the novel immune-based therapies that are currently used for treating HBV.

Key Words: Hepatitis B virus; Innate immunity; Adaptive immunity; Immune tolerance; Therapeutic strategy

Core Tip: Chronic hepatitis B (CHB) infection is an international health problem. Current clinical CHB treatment strategies can partly inhibit and eliminate hepatitis B virus (HBV), but cannot achieve long-lasting immune control of the virus. Persistent CHB infection arises as a consequence of the complex interactions between HBV and the host innate and adaptive immune systems. Therefore, it is important to understand the immunological mechanisms involved in CHB infection. In this review, we detail the immune biological characteristics and escape mechanisms of HBV and discuss novel immune-based therapies.

Citation: Zhao HJ, Hu YF, Han QJ, Zhang J. Innate and adaptive immune escape mechanisms of hepatitis B virus. *World J Gastroenterol* 2022; 28(9): 881-896
URL: https://www.wjgnet.com/1007-9327/full/v28/i9/881.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i9.881

INTRODUCTION

Hepatitis B virus (HBV) is a small hepatotropic, enveloped DNA virus. Hepatitis B is an international health problem caused by HBV infection. Currently, approximately 257 million people worldwide are chronic HBV carriers with a high risk of developing chronic liver diseases such as liver cirrhosis and hepatocellular cell carcinoma (HCC). Each year, approximately 1 million patients die of HBV-related liver diseases[1,2]. Current clinical treatment strategies for chronic hepatitis B (CHB) mainly include pegylated interferon-α (PEG-IFN-α) and nucleos(t)ide analogues (NAs). Unfortunately, current treatments have limitations and often fail to achieve long-term virologic control.

Generally, the host innate and adaptive immune systems play critical roles in eliminating HBV upon infection. However, HBV has evolved and developed efficient strategies for escaping host immune surveillance, which results in persistent infections. The majority of HBV infections occur in newborn infants with the presence of immunological defects, characterized by a lower quality and quantity of HBV-specific T cells and B cells. In addition, maternal hepatitis B e antigen (HBeAg) can induce the Kupffer cells (KCs) of the offspring by upregulating programmed death-ligand 1 (PD-L1) to suppress the HBV-specific $CD8^+$ T cells response to support HBV persistence after birth[3]. In addition, HBV circumvents endogenous type I interferon (IFN-I) responses[4] and inhibits the function of innate and adaptive immune cells[5]. Prolonged exposure of T cells to large quantities of viral antigens, such as hepatitis B surface antigen (HBsAg) and HBeAg, induces a defective T-cell response with the loss of effector functions and increased inhibitory receptor expression, facilitating viral persistence. Moreover, HBV infection affects the expression of human leukocyte antigen (HLA)-II alleles, including HLA-DP, HLA-DQ, and HLA-DR, on antigen-presenting cells (APCs)[6], which in turn impairs antigen presentation capacity with induction of an inefficient T-cell response, leading to persistent HBV infection.

The clinical outcomes of patients with CHB are highly based on the complex interactions between HBV and the host innate and adaptive immune systems. In this review, we detail the interaction between HBV and the host immune system to understand the immunological and biological characteristics of and escape mechanisms involved in CHB infection, and present the current immune-based therapies for CHB treatment.

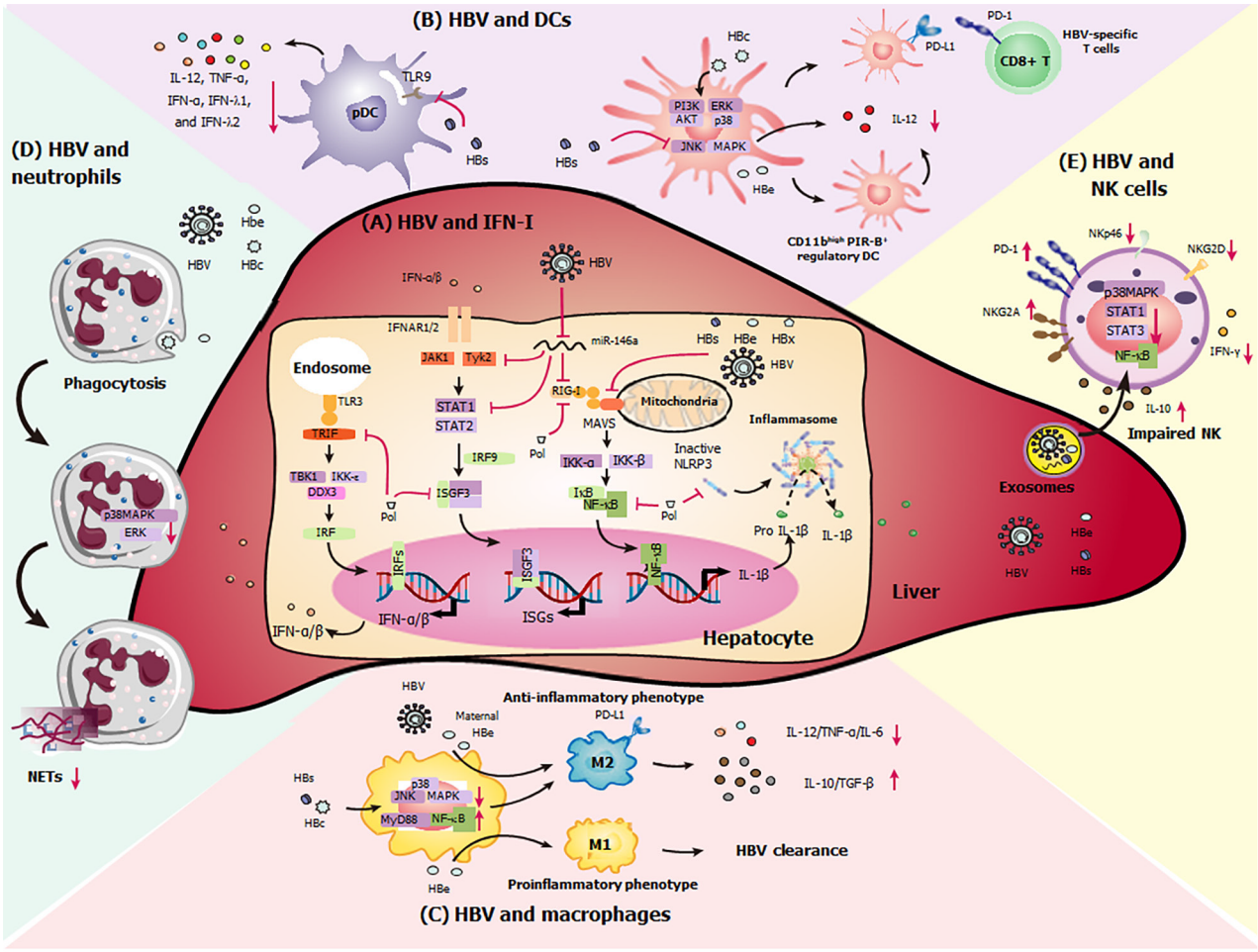
HBV ESCAPES INNATE IMMUNE SURVEILLANCE

Innate immune responses act as the first line of immune defense against viruses, bacteria, and tumors. Complement components, chemokines, and cytokines are soluble factors that form parts of the innate system. Granulocytes, dendritic cells (DCs), macrophages, mast cells, and natural killer (NK) cells are important effector cells[7,8]. Commonly, an effective innate immune response is initiated when pathogen-associated molecular pattern (PAMP) molecules bind pattern recognition receptors (PRRs), which stimulates chemokine and proinflammatory cytokine production, and innate immune cell activation, resulting in the elimination of viruses[9]. Here, we described the interaction between HBV and innate immunity (Figure 1).

HBV infection and IFN-I

PRRs, which are widely expressed by KCs, hepatic DCs, liver sinusoidal endothelial cells (LSECs), and hepatocytes, can recognize PAMPs from HBV and induce antiviral immune responses, resulting in the secretion and IFN-I and other inflammatory cytokines. IFN-I, as a major component of the innate immune response, is critical for HBV clearance. However, HBV circumvents endogenous IFN-I responses through multiple pathways to sustain persistent HBV infection.

Chronic HBV infection downregulates the expression of Toll-like receptor 3 (TLR3), retinoic acid-inducible gene I (RIG-I), and melanoma differentiation-associated protein 5 (MDA-5) in DCs and hepatocytes, leading to the reduction of responsiveness to PAMPs and impairment of IFN-I synthesis [10]. A previous study found that HBV infection upregulates microRNA-146a (miR-146a) expression in hepatocytes, inhibiting the expression of RIG-I-like receptors and in turn suppressing IFN-I transcription[11]. Additionally, HBsAg, HBeAg, HBx, and HBV virions themselves can inhibit IFN-β synthesis by downregulating mitochondrial antiviral signaling (MAVS) and interfering with the interaction between MAVS and RIG-I[12].



DOI: 10.3748/wjg.v28.i9.881

Figure 1 The interaction between hepatitis B virus and innate immunity. A: Hepatitis B virus (HBV) suppression of the type I interferon (IFN-I) response. HBV infection inhibits IFN-I transcription and signal transduction and IFN-β synthesis; B: HBV affects the function of dendritic cells (DCs). HBV upregulates programmed death-ligand 1 and induces regulatory DCs that exhibit extremely low T cell-stimulatory capacity and interleukin-12 production; C: HBV affects the function of macrophages. HBV-related antigens affect macrophage polarization (M1/M2), contributing HBV clearance or HBV persistence; D: HBV affects the function of neutrophils. HBV-related antigens decrease neutrophil extracellular trap release, which facilitates HBV immune escape, replication, and persistence; E: HBV affects the function of natural killer (NK) cells. HBV-related antigens and HBV-derived exosomes dampen the Retinoic acid-inducible gene I, nuclear factor kappa B, and p38 mitogen-activated protein kinase signaling pathways, resulting in the functional suppression of NK cells during chronic hepatitis B infection. DCs: Dendritic cells; DDX3: DEAD-box RNA helicase 3; ERK: Extracellular-regulated kinase; HBc: Hepatitis B core antigen; HBe: Hepatitis B envelope antigen; HBs: Hepatitis B surface antigen; HBx: HBV X protein; HBV: Hepatitis B virus; IFN-α: Interferon-α; IFN-β: Interferon-β; IFN-γ: Interferon-γ; IFN-I: Type I interferon; IFNAR: Interferon-α receptor; IKK-ε: IB kinase ε; IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-12: Interleukin-12; IRF3: Interferon regulatory factor 3; ISGs: Interferon-stimulated genes; ISGF3: Interferon-stimulated gene factor 3; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; M1: M1-like macrophages; M2: M2-like macrophages; MAPK: Mitogen-activated protein kinase; MAVS: Mitochondrial antiviral-signaling protein; miR-146a: microRNA-146a; MyD88: Myeloid differentiation primary response gene 88; NET: Neutrophil extracellular trap; NK: Natural killer; NKG2D: Natural killer group 2 member D; NKG2A: Natural killer group 2 member A; NF-B: Nuclear factor kappa B; PD-1: Programmed cell death protein 1; pDCs: Plasmacytoid DCs; PD-L1: Programmed death-ligand 1; PI3K: Phosphatidylinositol 3-kinase; Pol: Hepatitis B virus polymerase; Pro-IL-1β: IL-1β precursor; RIG-I: Retinoic acid-inducible gene I; STAT1: Signal transducer and activator of transcription 1; STAT2: Signal transducer and activator of transcription 2; TBK1: TANK-binding kinase 1; TGF-β: Transforming growth factor-β; TLR2: Toll-like receptor 2; TLR3: Toll-like receptor 3; TLR9: Toll-like receptor 9; TNF-α: Tumor necrosis factor-α; TRIF: Toll/IL-1 receptor domain-containing adaptor inducing IFN-β; Tyk2: Tyrosine kinase 2.

Binding of IFN-I to the IFN receptor can induce the activation of IFN-stimulated genes (ISGs), thereby directly inhibiting HBV infection. However, HBV can extensively impair IFN-I-induced signal transduction and dampen IFN-I-mediated immune responses[4]. HBx is able to reduce transcription of the IFN-α receptor (IFNAR1) and downregulate tyrosine kinase 2, which is essential for cell surface IFNAR1 expression[13]. Additionally, matrix metalloproteinase 9, which is increased in the peripheral blood mononuclear cells of patients with CHB, binds to IFNAR1 and facilitates its phosphorylation, ubiquitination, subcellular distribution, and degradation[14]. HBV can inhibit the activities of IFN-stimulated response elements with lower ISG expression by disrupting the intracellular Janus kinase–signal transducer and activator of transcription 1 (STAT1) signaling pathway. HBV-induced miR-146a downregulates cellular STAT1 levels and blocks STAT1-Tyr701 phosphorylation in hepatocytes[11]. HBV polymerase interferes with the binding of DEAD-box helicase 3 X-linked (DDX3) to the TANK-binding kinase 1/IκB kinase epsilon complex and the induction of IFN-stimulated gene

factor 3 (ISGF3) to inhibit IFN-β induction[10]. In addition, HBV polymerase suppresses interleukin 1 beta (IL-1β) production by inhibiting nuclear factor kappa B (NF-κB) signaling and the inflammasome-caspase-1 pathway, resulting in IFN-α resistance and persistent HBV infection[15].

Based on these findings, IFN-I is used for the treatment of CHB. IFN-α-mediated HBV suppression is correlated with the levels of apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (known as APOBEC) and the base excision repair gene Nei endonuclease VIII-like 3[16]. IFN-α can also epigenetically regulate the HBV covalently closed circular DNA (cccDNA) minichromosome by disrupting general control non-depressible 5-mediated histone H3 lysine 79 methylation succinylation, resulting in the clearance of HBV cccDNA[17]. Imam *et al*[18] identified sterile alpha motif domain containing 4A as an important anti-HBV ISG that binds to and triggers degradation of the unidentified Smaug-recognition region sequence in viral RNA. ISG20 can induce the degradation of HBV RNA by selectively recognizing and binding N6-methyladenosine. In addition, tripartite motif containing 5 gamma suppresses HBV replication by interacting with the HBx protein, which promotes HBx ubiquitination at residue K48 and its subsequent degradation[19]. MX dynamin like GTPase 2 reduces HBV cccDNA by indirectly impairing the conversion of relaxed circular DNA to cccDNA[20]. Interestingly, IFN-α can also induce soluble factors that compete with HBV for binding to heparin glycosaminoglycans, thereby inhibiting HBV infection[21]. In addition to its direct antiviral effects on HBV, IFN-I indirectly exerts antiviral functions by activating immune cells. IFN-I can quickly recruit and activate NK cells and DCs, promoting the initiation of adaptive immunity[5,22], which in turn contributes to the elimination of HBV.

HBV infection and DCs

As professional APCs, DCs serve as a bridge between the innate and adaptive immune responses[23]. Recent data have shown that functional impairment of DCs by HBV infection fails to induce efficient anti-HBV immunity, leading to CHB infection and the progression of liver disease[24]. Previous data have demonstrated that patients with CHB have significantly fewer peripheral blood DCs than control subjects, accompanied by a functional decline and directly causing HBV-specific T cell dysfunction[24]. Compared to those of healthy donors, myeloid DCs (mDCs) isolated from patients with CHB display limited antigen-presenting capacity and migration capacity, features that are accompanied by the decreased expression of interleukin 6 cytokine family signal transducer (also known as gp130)[24]. Persistent HBV infection downregulates cluster of differentiation 80 (CD80), CD83, CD86, and CD40 expression in DCs, which suppresses the transduction of costimulatory signals to T cells. In addition, HBsAg reduces IL-12 production by mDCs by disrupting the c-Jun N-terminal kinase (JNK)–mitogen-activated protein kinase (MAPK) pathway, resulting in a markedly tolerogenic phenotype[25]. HBcAg upregulates programmed death-ligand 1 (PD-L1) by activating the phosphoinositide 3-kinase (PI3K)–AKT, extracellular-regulated kinase (ERK), and p38 signal transduction pathways, which suppresses HBV-specific T cell immune function[26]. HBeAg induces the conversion of bone marrow-derived DCs into $CD11b^{hi}$PIR-B^{+} regulatory DCs, which exhibit extremely low T-cell stimulatory capacity and IL-12 production[27]. Furthermore, HBV particles, especially HBsAg, downregulate TLR expression and abrogate TLR9-triggered maturation of plasmacytoid DCs, resulting in the significantly decreased secretion of certain cytokines such as IL-12, tumor necrosis factor alpha (TNF-α), IFN-α, IFN-λ1, and IFN-λ2[28-30]. In addition, chronic HBV infection impairs IFN-α secretion and pDC maturation in response to TLR7 ligands[28].

HBV infection and macrophages

Macrophages are important innate immune cells that fight against pathogen infection and can interact with lymphocytes by activating and inhibitory surface molecules. HBV can affect the functions of monocytes and macrophages, thereby contributing to persistent HBV infection. HBV infection promotes the activation of anti-inflammatory macrophages with increased IL-10 production, which support the functional inactivation of $CD8^{+}$ T cells.

KCs, which are localized in liver sinusoids, are the largest population of innate immune cells in the liver[31]. They are stationary and able to effectively phagocytose cellular debris, foreign material, or pathogens, acting as critical sentinels for liver homeostasis[32]. Chronic HBV infection induces the production of immunomodulatory mediators such as IL-10 and transforming growth factor beta (TGF-β), and the expression of PD-L1 and PD-L2 by KCs, suppressing anti-HBV T cell responses. Furthermore, upon HBV infection, elderly mice have a significantly higher number of TNF-α-producing $Ly6C^{+}$ monocytes and a much lower number of IL-10-secreting KCs than younger mice, facilitating HBV clearance[33]. However, KCs can play different roles in the presence of different HBV antigens[34]. Boltjes *et al*[35] found that KCs could interact with HBsAg, which induced secretion of the proinflammatory cytokines IL-6 and TNF that was substantially increased compared with that seen in healthy controls. *In vivo* experiments have demonstrated that HBcAg interacts with KCs upon TLR2 activation, mediating humoral and cellular tolerance *via* IL-10 production during CHB infection, and TLR2 knockout or KC depletion leads to an accelerated HBV clearance and improved HBV-specific $CD8^{+}$ T cell responses[36]. HBeAg suppresses lipopolysaccharide-induced NOD-, LRR- and pyrin domain-containing protein 3 activation and IL-1β maturation in KCs by inhibiting NF-κB phosphorylation and reactive oxygen species production[37]. Nonetheless, HBeAg can play two distinct roles in macrophage

function. Upon HBV infection, maternal HBeAg enhances PD-L1 expression in KCs with an M2-like anti-inflammatory phenotype, which suppresses the HBV-specific cytotoxic T lymphocyte (CTL) response and leads to HBV persistence; however, in control mice born to HBeAg-negative mothers, HBeAg promotes the M1 proinflammatory phenotype, contributing to HBV clearance[3].

Except for KCs, monocyte-derived macrophages are critical for regulating the anti-HBV immune response and disease pathogenesis during HBV infection. Intrahepatic macrophages that had phagocytosed HBcAg show anti-inflammatory over proinflammatory functions and favor the maintenance of infection. In addition, HBsAg inhibits TLR2-induced phosphorylation of p38 MAPK and JNK MAPK with reduced production of IL-6, TNF-α, and IL-12 in human monocytes[38]. Previous findings have also shown that HBsAg can interact with monocytes and induce the MyD88–NF-κB-signaling pathway with high expression of the inhibitory molecules PD-L1, IL-10, and TGF-β, thereby initiating an immunosuppressive cascade[39]. In contrast to HBeAg and HBsAg, HBcAg from HBV-infected hepatocytes upregulates IL-23 secretion in monocyte-derived macrophages and enhances macrophage-mediated angiogenesis[40]. In addition, HBV-induced M2-like macrophages promote the immunosuppressive activity of regulatory T (Treg) cells by enhancing cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), inducible T cell costimulator, and CD39 expression levels in an amphiregulin-dependent manner[41], impairing T helper type 1 cell immune responses and accelerating liver fibrosis and pathology.

HBV infection and neutrophils

Neutrophils exhibit protective functions against microbial infections *via* phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs). Recent results have shown that HBV might suppress the neutrophil response. For example, neutrophils from patients with liver cirrhosis show a decreased capability for NET release, accompanied by the reduced expression of CD69 and CD80[42]. Additionally, HBV-related antigens, such as HBeAg and HBcAg, decrease NET release by decreasing p38 MAPK and ERK phosphorylation and autophagy, which facilitates HBV immune escape, replication, and persistence[43].

HBV infection and NK cells

As the main effector cells of the innate immune system, NK cells constitute up to 40%–50% of human liver lymphocytes, and serve as the first line of defense against pathogens. Activated cytolytic $CD56^{dim}$ NK cells expressing NKp46, NKp30, and perforin are associated with efficient HBV containment[44,45]. Additionally, antibody-mediated activation of NK cells plays a vital role in resolving HBV infection[45]. Abnormal NK cell receptor expression and hepatic NK cell dysfunction contribute to persistent CHB infection and HCC progression, which are related to the poor prognosis and survival of patients with liver cancer[46]. The levels of activating receptors (*e.g.*, NKp30, NKp46, and natural killer group 2 member D [NKG2D]) and cytokines (*e.g.*, IFN-γ and TNF-α) are significantly decreased in patients with CHB, which is accompanied by the higher secretion of inhibitory NK cell receptors such as T cell immunoglobulin and mucin domain-containing protein 3 (Tim-3), NKG2A, and IL-10[47]. In addition, the decreased expression of CD122, the common β chain of the IL-2 receptor on $CD56^{dim}$ NK cells, is associated with NK cell dysfunction during CHB infection[48].

The roles of circulating HBV-related antigens (*e.g.*, HBsAg and HBeAg) in mediating NK cell inhibition remain unclear. Recently, we found that HBsAg and HBeAg directly interact with NK cells and act as inhibitory mediators by interfering with the activation of STAT1, NF-κB, and p38 MAPK, which in turn impairs NK cell cytotoxicity and cytokine production[49]. HBsAg downregulates STAT3 expression, which is partially correlated with degranulation and cytokine production in patients with HBeAg-negative CHB[50]. Additionally, HBsAg-treated monocytes promote the conversion of NK cells into IL-10-producing regulatory NK cells *via* PD-L1 and major histocompatibility complex, class I, E signals, which contribute to persistent CHB infection[39]. Importantly, exosomes derived from patients with CHB shuttle HBV nucleic acids into NK cells and then dampen the RIG-I, NF-κB, and p38 MAPK signaling pathways, resulting in the functional suppression of NK cells during CHB infection[51]. miR-146a is significantly elevated in patients with CHB and modulate both NK and T-cell responses[52]. Interestingly, we found that miR-146a in NK cells can be induced by exogenous IL-10 and TGF-β, which in turn leads to NK cell dysfunction by directly targeting STAT1, accompanied by weakened IFN-γ and TNF-α secretion in patients with CHB[53].

HBV ESCAPES ADAPTIVE IMMUNE SURVEILLANCE

Adaptive immunity plays a critical role in HBV infection, accompanied by antigen specificity and sustained memory responses. Under the stimulation of APCs, HBV-specific $CD4^+$ T cells and $CD8^+$ T cells are activated and then secrete antiviral cytokines such as IL-12, IFN-γ, and TNF-α, and induce CTL responses to kill HBV-infected hepatocytes[54]. In addition, follicular helper T (Tfh) cells promote B cell differentiation into plasma cells, which are capable of producing HBV-specific antibodies[55]. Recent studies have demonstrated that newborn infants have immunological defects, and the inability to

induce HBV-specific T- and B-cell responses have been found in neonatal animals, which develop chronic HBV infection[3,56]. Furthermore, chronic HBV infection can suppress the adaptive immune system and dampen HBV clearance, leading to persistent HBV infection in patients with CHB.

HBV infection and HLA-II

HLA in APCs plays a critical role in initiating the host antiviral immune response against HBV infection due to its capacity to attract and bind peptides. HLA-I molecules can present HBV peptides to $CD8^+$ cytotoxic T lymphocytes, resulting in the direct cytolysis of HBV-infected hepatocytes. HLA-II alleles, including HLA-DP, HLA-DQ, and HLA-DR, encode MHC-II molecules that present exogenous antigens to $CD4^+$ T cells[57,58]. Different HLA-II alleles with particular amino acid polymorphisms determine which peptides can be presented to T cells. Moreover, these HLA alleles expressed on APCs contribute to presenting a broad range of peptides, thus determining the variability in the host immune response to HBV. Compared to HLA-DP and HLA-DQ, HLA-DR allele containing an extra β-chain gene whose product can pair with the DRα chain on APCs, is more important for the induction of sustained HBV-specific immune response. Upon HBV infection, single nucleotide polymorphisms of HLA-II antigens may also contribute to the induction of immune tolerance, leading to persistent HBV infection[57,59-62]. HBV infection reduces the expression of HLA-DP and HLA-DQ molecules on APCs, which in turn results in impaired antigen presentation capacity and an inefficient T-cell response[12,13]. Thus, polymorphisms of HLA-II genes during HBV infection can alter the antigen-binding properties of HLA-II and affect the HBV-specific immune response, partly promoting the persistent HBV infection.

HBV infection and $CD8^+$ T cells

HBV-specific $CD8^+$ T cells function as key cellular effectors against HBV infection[63]. During CHB infection, $CD8^+$ T cells encounter HBV antigens presented by intrahepatic APCs, such as DCs, KCs, or LSECs with weakened costimulatory signals, resulting in immune tolerance[64]. In addition, HBV infection can cause deficient secretion of inflammatory cytokines such as IL-12 and IFN-α/β in response to PAMP stimulation, further dampening the third signal required for $CD8^+$ T-cell activation. Additionally, sustained exposure to high doses of HBV antigens (*e.g.*, HBsAg and HBeAg) leads to exhausted T cells and impaired effector functions during CHB infection. Microarray analyses have revealed that HBV significantly upregulates the expression of the proapoptotic molecule Bcl-2-like protein 11 among HBV-specific $CD8^+$ T cells, suggesting a key mechanism related to the depletion of $CD8^+$ T cells during CHB infection[65]. Exhausted $CD8^+$ T cells show reduced IL-2, IFN-γ, and TNF-α secretion and lost cytotoxic and proliferative capacities[66,67]. Moreover, exhausted HBV-specific $CD8^+$ T cells display multiple inhibitory receptors such as PD-1, CTLA-4, CD244 (2B4), Tim-3, and lymphocyte activation gene 3[68], closely mimicking the transcriptional profiles of $CD8^+$ T cells[67,69,70].

T-bet is essential for successful $CD8^+$ T cell responses against HBV, whereas eomesodermin (EOMES) is a key driver of T cell exhaustion during chronic HBV infection[67,69,71]. Schurich *et al*[71] observed that reduced PD-1 expression on HBV-specific $CD8^+$ T cells is accompanied by high levels of T-bet, which can increase $CD8^+$ T cell functions[71], whereas EOMES might compensate for the lack of T-bet expression during HBV infection[67]. Data from a recent study showed that exhausted $CD8^+$ T cells express elevated levels of the transcription factors interferon regulatory factor 4, basic leucine zipper ATF-like transcription factor, and nuclear factor of activated T cells 1, which in turn promote the expression of multiple inhibitory receptors (such as PD-1) and is accompanied by impaired antiviral function and cellular metabolism. However, transcription factor T cell factor 1 (TCF1) expression is repressed in exhausted $CD8^+$ T cells, which is important considering that TCF1 is essential for memory T cell differentiation[72]. Moreover, when compared with HBV core-specific $CD8^+$ T cells, HBV polymerase-specific $CD8^+$ T cells show higher expression of CD38 and EOMES, accompanied by lower T-bet expression and a reduced expansion capacity[70]. Recently, transcriptome analysis of exhausted HBV-specific $CD8^+$ T cells in patients with CHB revealed a lower mitochondrial potential and substantial mitochondrial dysfunction[73,74], whereas exposure to antioxidants or IL-12 partially reinvigorated the antiviral activity of HBV-specific $CD8^+$ T cells[73,74].

$CD4^+$ T cells

$CD4^+$ T cells are important in regulating $CD8^+$ T cell activation, proliferation, and memory responses during HBV infection[75]. Generally, a loss help of $CD4^+$ T cells is considered the major factor involved in HBV-specific CTL cell failure[76]. Increasing attention has been given to the exhaustion of $CD4^+$ T cells during CHB infection. Previous results have demonstrated that HBV-related antigens, such as HBcAg and HBsAg, can upregulate the expression of inhibitory molecules on $CD4^+$ T cells. For example, Li *et al*[77] found that HBcAg increased PD-1 expression on $CD4^+$ T cells *via* the JNK, ERK, and PI3K/AKT signaling pathways disrupt the function of $CD4^+$ T cells. HBsAg increased the expression of human protein inhibitor of activated STAT1 expression (which is dependent on activation of the ERK and p38 MAPK signaling pathways), thereby contributing to the ineffectiveness of traditional treatments for CHB patients[78]. Data from a recent study showed that $CD4^+$ T cells in patients with CHB expressed high levels of TRAIL receptors, and these T cells could be targeted by $TRAIL^+$ NK cells, leading to a reduction in the number of $CD4^+$ T cells[79]. Additionally, the decreased secretion of

proinflammatory cytokines (such as IL-2, IFN-γ, and IL-21) by HBV-specific $CD4^+$ T cells contribute to the exhaustion of $CD8^+$ T cell responses during chronic HBV infection[80]. $CD4^+$ T cells also differentiate into $CD4^+$ $CD25^+$ $Foxp3^+$ Treg cells, which secrete the suppressive cytokines IL-10 and TGF-β, resulting in a progressive loss of HBV-specific $CD8^+$ T cells[81]. Thus, $CD4^+$ T cells can directly influence HBV clearance by regulating $CD8^+$ T cells.

Tfh cells express C-X-C chemokine receptor type 5 (CXCR5) and can specifically recognize and bind to follicular B cells expressing CXCL13, which promote the formation of affinity-matured, long-lived plasma cells and antibody secretion[82]. A deficiency of Tfh cells can inhibit the formation of germinal centers (GCs) in the spleen[83]. Thus, Tfh cells play important roles in orchestrating the humoral immune response and HBsAg seroconversion in patients with CHB[84]. Previous results have shown that the frequency of Tfh cells correlates negatively with HBsAg levels in patients with CHB after PEG-IFN-α therapy[85]. The recovery of Tfh cell responses induces the production of anti-HBs antibodies and accelerates HBV clearance[55]. Additionally, Wang *et al*[86] found that HBV infection significantly increases the proportion of $CD4^+$ $CXCR5^+$ $CD25^+$ $Foxp3^+$ follicular regulatory T (Tfr) cells. Compared to $CD25^-$ Tfh cells, $CD25^+$ Tfh cells express high levels of inhibitory receptors, such as PD-1 and CTLA-4, with lower levels of IFN-γ and IL-17 and higher TGF-β secretion. Importantly, Tfr cells can suppress the GC reaction of B cells and the antiviral effect of $CD8^+$ T cells. Therefore, Tfh cell dysfunction might disrupt humoral immune responses during CHB infection.

B cells

Anti-HBs antibodies are protective antibodies that can prevent HBV from entering into host hepatocytes and can clear infectious HBV particles from the body[87,88], and B cells are essential for effective HBV control. Although the total number of B cells is enriched during CHB infection[89], previous data revealed that patients with CHB showed a decreased frequency of HBsAg-specific B cells[90]. Furthermore, the production of anti-HBs was defective in patients with CHB[91]. Recent findings indicate that hyperactivated B cells with increased expression of CD69 and CD71, have deficient proliferative capacity and are unable to achieve HBsAg seroconversion in CHB patients.

Burton *et al*[92] found that HBsAg-specific B cells in patients with CHB exhibited a $CD21^-$ $CD27^-$ atypical memory B cell (atMBC) phenotype, which was accompanied by high levels of inhibitory receptors such as PD-1, BTLA, and CD22. atMBCs exhibit impaired survival, proliferation, and cytokine production and cannot normally differentiate into antibody-producing plasma cells, which dampens humoral immune responses in patients with CHB. Poonia *et al*[93] found that HBcAg binding to B cells can induce high expression of the inhibitory receptors Fc receptor-like 5 (FcRL4) and FcRL5 on B cells, as well as dysfunctional phenotypes, and can also suppress the proliferation and activation of B cells mediated by the B cell receptor and TLR signaling. Additionally, HBcAg drives B cell differentiation into IL-10-producing regulatory B (Breg) cells characterized as $CD19^+$ $CD24^{hi}$ $CD38^{hi}$, which suppresses $CD8^+$ T cell responses[89]. Moreover, Breg cells have also been found to promote the conversion of $CD4^+$ $CD25^-$ effector T cells into $CD4^+$ $CD25^+$ Treg cells, thereby participating in the maintenance of immune tolerance during chronic HBV infection[89].

In addition to antibody production, B cells are also considered professional APCs during CHB infection. However, the levels of costimulatory molecules (CD80 and CD40) are significantly decreased in circulating B cells, which might impair the interactions between B cells and effector T cells, thus inducing T cell exhaustion[94]. B cells can also regulate the immune response by secreting cytokines during CHB infection. HBeAg can stimulate B cell activation by promoting B-cell activating factor production *via* IL-6 and IFN-γ secretion[95,96], where IL-6 can play a non-cytolytic antiviral role against HBV by inducing cccDNA decay, reducing HBV transcription, and downregulating the NTPC receptor [97].

NOVEL IMMUNE THERAPEUTIC STRATEGIES FOR HBV

Current CHB treatments fail to cure HBV and are often accompanied by serious side effects. The long-term use of HBV drugs may even lead to mutations in HBV polymerase and cause drug resistance[98, 99]. Therefore, to overcome the limitations of clinical CHB therapy, researchers are developing new immune strategies to achieve sustained virologic remission (Table 1).

Monoclonal antibodies

Sustained exposure to a high load of viral antigens leads to T cell exhaustion in patients with CHB. Serum HBsAg levels can be as high as 400 μg/mL in patients with CHB; thus, this phenomenon can play a key role in inhibiting HBV-specific immune responses. Neutralizing antibodies against HBsAg or preS1 eliminated HBV and restored HBV-specific immune responses to preventative HBV vaccines in HBV carrier mice. Gao *et al*[100] identified a novel monoclonal antibody (E6F6) that targets the HBsAg-aa119-125 peptide, which can mediate long-lasting HBsAg clearance and facilitates the HBV-specific T cell response *via* Fc-gamma receptor-mediated phagocytosis. Multiple release inhibitors and monoclonal antibodies against HBsAg have been tested in clinical trials, such as GC1102 (a recombinant human

Table 1 Novel immune therapeutic strategies for clinical chronic hepatitis B treatment

Target	Drug name	Sponsor	Phase	Notes	Ref.
HBsAg inhibitor	REP-2139	Replicor	II	Reduce the level of HBsAg	[101,102]
HBsAg inhibitor	REP-2165	Replicor	II	Reduce the level of HBsAg (similar to REP-2139)	[102]
RIG and NOD agonist	SB9200	Spring Bank	IIb/III	Prolonged IFN-α and IFN-β secretion; Reduce hepatitis virus antigen and DNA	[107]
TLR7 agonist	RO7020531	Roche	I	Activate HBV-specific CD8+ T and Tfh cells; Reduce the frequency of Tregs and MDSCs	[108]
TCR-T cells	HBsAg-TCR-T cells	Lion TCR Pte	I	Safely and efficiently reduced HBsAg levels; Reduced level of HBV DNA and HBsAg	[115]
Therapeutic vaccine	TG1050	Transgene	I	Reduced level of HBV DNA and HBsAg; Long-lasting HBV-specific T cell responses	[125]
Therapeutic vaccine	HBsAg-HBIG (YIC)	National Vaccine and Serum Institute	III	Increase the level of IL-2; Long-lasting HBV-specific T-cell responses	[126]
Therapeutic vaccine	Nasvac	CIGB	III	Sustained control of HBV DNA; Clearance of HBeAg	[127]
Therapeutic vaccine	GS-4774	Gilead	III	Strong immune stimulatory effect on T cells	[128]

HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; NOD: nucleotide-binding oligomerization domain; IFN-α: Interferon-α; IFN-β: Interferon-β; IL-2: Interleukin-2; MDSCs: Myeloid-derived suppressor cells; RIG-I: Retinoic acid-inducible gene I; TCR: T-cell receptor; Tfh: Follicular helper T cells; TLR7: Toll-like receptor 7; Tregs: Regulatory T cells.

monoclonal anti-HBs antibody, Green Cross, phase II/III), EYP001 (farnesoid X receptor agonist, Enyo Pharma, phase II), REP-2139 (Replicor, phase II)[101,102], REP-2165 (Replicor, phase II)[102], and RG7834 (Roche, pre-clinical)[103].

Cytokines

Cytokines have been widely used as immunomodulatory agents to regulate immune responses during CHB treatment. For example, IL-12 administration alone can induce IFN-γ secretion and the recovery of exhausted $CD8^+$ T cells in patients with CHB[71]. Moreover, employing IL-12 as an adjuvant combined with the recombinant HBV vaccine (rHBVvac) elicits systemic HBV-specific $CD4^+$ and $CD8^+$ T cell responses and restores HBsAg-specific humoral immunity, thereby overcoming immune tolerance in patients with CHB[104]. Recent findings have shown that co-administering GM-CSF with the rHBVvac induces the secretion of HBsAg-specific IFN-γ and CTL responses to clear HBV *in vivo*[105]. In addition, IL-2, IL-15, IL-21, and IL-33 also efficiently clear persistent HBV infection and produce a long-term immune response against HBV reinfection[106].

TLR and RIG-I agonists

Currently, various TLR ligands are used as drugs for clinical CHB therapy, such as SB9200 (Spring Bank, phase IIb/III)[107], RG-7795 (Roche, phase II), RO7020531 (Roche, phase I)[108], GS-9620 (Gilead, phase II), GS-9688 (Gilead, phase II), RG-7854 (Roche, phase I), and JNJ-4964 (Janssen, preclinical). Data from previous studies have shown that GS9620 (a TLR7 agonist) can upregulate IFN-α production, restore the effector functions of $CD8^+$ T cells and NK cells, and decrease HBsAg and HBeAg titers. Single-stranded RNA40 (a TLR8 agonist) can selectively induce IL-12, IL-18, and IFN-γ secretion by monocytes in patients with CHB, which is beneficial for HBV clearance[109]. SB9200, an agonist of RIG-I and nucleotide binding oligomerization domain containing 2, can stimulate prolonged IFN-α and IFN-β secretion and ISG activation and efficiently reduce hepatic woodchuck hepatitis virus antigen and DNA levels in infected woodchucks[107]. Interestingly, compared with entecavir administration, SB9200 pretreatment better reduces HBV virion production[110]. Additionally, we found that a small interfering RNA targeting HBx (3p-siHBx) induced RIG-I activation, which improved the immune microenvironment and triggered the activation of NK cells and $CD8^+$ T cells in HBV-carrier mice[111].

Immune checkpoint blockade

Prolonged exposure to HBV leads to NK cell dysfunction and hyperexpression of immune checkpoint proteins in T cells. As an alternative approach, blocking the inhibitory receptor NKG2A increases the activity of human NK cells to promote HBsAg clearance[112]. In addition to direct anti-HBV effects,

recent data have shown that NK cells in patients with CHB selectively inhibit HBV-specific T cell responses *via* an IL-10-dependent pathway[39]. Furthermore, NK cells in NA-treated CHB patients expressing high levels of death receptor ligands, such as TNF-related apoptosis inducing ligand (TRAIL) or NKG2D, can mediate the lysis of activated T cells, thereby contributing to the development of chronic HBV infection[46,49]. Depleting inhibitory NK cells and blocking the NKG2D and TRAIL pathways during NA treatment further induces significant improvements in terms of HBV-specific T cell functions to achieve an HBV cure[79]. Additionally, blocking inhibitory receptors, such as PD-1, 2B4, and Tim-3, can restore exhausted HBV-specific $CD8^+$ T cells by promoting the recovery of cytotoxicity, cytokine production, and proliferation, offering an excellent opportunity to achieve sustained virologic control[113].

T cell receptor/chimeric antigen receptor T cells

The adoptive transfer of autologous T cells, such as chimeric antigen receptor (CAR) T cells, is another promising immunotherapeutic option for HBV therapy. These CAR T cells can directly recognize HBV antigens on infected hepatocytes and HBV-related HCC cells independently of HLA, without any need for antigen processing and presentation[114]. Qasim *et al*[115] found that genetically modified T cell receptor (TCR) T cells safely and effectively targeted HBsAg and reduced HBsAg levels in a patient with HBV-related HCC who had undergone liver transplantation. As an alternative strategy, CAR T cells expressing a recombinant HBsAg-specific antibody together with CD28 and CD3 zeta could also recognize and eliminate HBsAg-positive hepatocytes *in vitro*. Moreover, HBsAg-CAR-$CD8^+$ T cells localized to the liver and rapidly reduced HBV replication without significant liver damage after adoptive transfer in a transgenic mouse model of HBV[116]. Additionally, HBsAg-CAR T cells specifically decreased plasma HBsAg, HBV-DNA, and HBV core-positive hepatocytes in persistently HBV-infected chimeric mice with humanized livers after adoptive transfer of HBsAg-CAR-T cells[117], thereby providing a potential therapeutic approach for HBV.

However, specific challenges related to TCR or CAR T-cell therapy remain for HBV treatment, including the risk of developing severe liver damage and the suppressive effects of transferred TCR/CAR T cells due to the immune tolerance of the liver. To prevent severe side effects, such as liver damage and uncontrolled proliferation, Kah *et al*[118] developed a method for transient mRNA electroporation into engineered HBV-TCR T cells. In a separate study, PD-1 knockdown in HBV-TCR-T cells increased their effector functions and ability to kill tumor cells in the PD-$L1^{hi}$ liver microenvironment [119]. In addition, engineered CAR T cells to overexpress c-Jun, an AP-1 transcription factor, showed enhanced expansion and functional capacity with improved antitumor efficiency[120]. These findings have facilitated the development of TCR/CAR T cells for clinical CHB treatment.

Therapeutic vaccines

Therapeutic vaccination presents an attractive strategy for HBV eradication. A novel hepatitis B therapeutic vaccine could overcome immune tolerance; effectively induce powerful $CD4^+$ T cells, $CD8^+$ T cells, and humoral immune responses; and ultimately achieve sustained control of CHB infection. Kosinska *et al*[121] proposed approaches for developing safe and effective therapeutic vaccines, including: Designing potent vaccine components or schemes to prime antigen-specific immune responses; combining checkpoint inhibitors with other strategies to restore exhausted T cells; and Reducing HBV-related antigen levels to prevent T cell attrition and exhaustion. Based on this guidance, we prepared HBsAg nanogels (Ng) with chitosan (CS) and poly γ-glutamic acid (γ-PGA). Interestingly, we found that single-dose HBsAg CS-γ-PGA Ng immunization, especially HBsAg Ng (+), enhanced DC maturation and induced HBV-specific cellular and humoral immunity, and promoted the generation of effector memory T cells for HBV clearance[122]. Recent data also showed that a ferritin NP-preS1 vaccine manifested an efficient antibody response, resulting in efficient viral clearance by delivering preS1 to $SIGNR1^+$ DC[123]. Additionally, we demonstrated that employing poly I:C as an adjuvant combined with rHBVvac also efficiently and safely decreased HBV DNA, HBV RNA, and HBsAg in an HBV carrier mouse model. Importantly, we found that the therapeutic vaccine partially reversed immune tolerance and promoted HBV-specific $CD8^+$ T cell terminal differentiation into $KLRG1^+$ effector T cells, thereby playing a crucial role in HBV clearance[124].

Multiple therapeutic vaccines have been developed and administered for CHB treatment with different clinical outcomes. TG1050, a novel HBV-targeted immunotherapeutic vaccine based on a non-replicative adenovirus vector encoding multiple HBV antigens (S, core, and polymerase), effectively induced polyfunctional and long-lasting HBV-specific T cell responses and reduced HBV DNA and HBsAg levels *in vivo*. The results of a phase Ib trial showed that TG1050 induced the production of IFN-γ-producing HBV-specific T cells and safely achieved effective viral suppression[125]. Currently, TG1050 is being investigated in phase II clinical trials and may be a very promising therapeutic vaccine for HBV, especially in combination with TLR9 agonists. Additional therapeutic HBV vaccines under investigation in clinical trials worldwide including HBsAg-HBIG ("YIC", National Vaccine and Serum Institute, phase III)[126], Nasvac (CIGB, phase II/III)[127], GS-4774 (Gilead, phase II)[128], HepTcell (Altimmune, phase Ib), AIC 649 (AiCuris, phase I), INO-1800 (Inovio, phase I), HB-110 (Ichor, phase I), JNJ-64300535 (Janssen, phase I), TomegaVax HBV (TomegaVax, preclinical), and VR-CHB01 (Vical, preclinical).

CONCLUSION

PEG-IFN-α and NAs are the current major treatment strategies for CHB. Although these antiviral drugs can partly inhibit and eliminate HBV, viral breakthroughs may result from non-adherence due to limitations such as the high cost, the emergence of viral resistance, a long treatment cycle, and adverse side effects. Ideal anti-HBV strategies should meet the following criteria: the strong ability to inhibit virus replication with low drug resistance; stimulation of antiviral immune responses; Long-lasting effects without recurrence; and eventual removal of the virus. Therefore, the design of novel strategies to clear HBV and achieve long-lasting immune control remains a challenging task. Persistent CHB infection arises as a consequence of the complex interactions between HBV and the host innate and adaptive immune systems. Therefore, understanding the immunological mechanisms involved in CHB infection is important for designing potential therapeutic strategies for clinical CHB treatment. In this review, we detailed the immune biological characteristics and escape mechanisms of HBV and discussed novel immune-based therapies. Targeting a combination of viral and host factors provides the best possible chance for achieving a functional cure for CHB.

FOOTNOTES

Author contributions: Zhao HJ and Zhang J designed the structure of this review; Zhao HJ wrote the paper; Hu YF contributed to the literature review; Zhao HJ, Han QJ, and Zhang J revised the paper; All authors approved the final version.

Supported by National Science Foundation for Young Scientists of China, No. 82001687; National Major Science and Technology Project for Control and Prevention of Major Infectious Diseases, No. 2018ZX10301401; National Postdoctoral Program for Innovative Talents, No. BX20190192; China Postdoctoral Science Foundation, No. 2020M672064; and National Basic Research Program of China, No. 2013CB531503.

Conflict-of-interest statement: The authors have no potential conflicts of interest to declare.

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S-Editor: Vasudevan A
L-Editor: Filipodia
P-Editor: Ma YJ

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