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Hepatitis B virus-persistent infection and innate immunity defect: Cell-related or virus-related?

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Abstract

The outcomes of hepatitis B virus (HBV) infection are closely related to the age at which infection was acquired. Infection acquired in adult life tends to be self-limited, in contrast to perinatal acquirement, for which chronic persistence of the HBV is a general outcome. Innate immunity plays an indispensable role in early virus infection, facilitating virus clearance. However, it has been reported that HBV is under-recognized and poorly eliminated by the innate immune system in the early stages of infection, possibly explaining the long-lasting persistence of viremia afterwards. Furthermore, due to the existence of covalently closed circular DNA, chronic HBV clearance is very difficult, even when patients are given interferon- α and nucleotide/nucleoside analogs for antiviral therapy. The mechanism by which HBV evades innate immune recognition and establishes persistent infection remains a subject of debate. Besides, some researchers are becoming more interested in how to eradicate chronic HBV infection by restoring or boosting innate immunity. This review aimed to summarize the current knowledge on how intrahepatocyte signaling pathways and innate immune cells act after the onset of HBV infection and how these actions are related to the persistence of HBV. We anticipate the insights presented herein to be helpful for future development of novel immune therapeutic strategies to fight HBV infection.

Key words: Hepatitis B virus; Innate immunity; Immune evasion; Pattern recognition receptor; Toll-like receptor;

Natural killer cells; Kupffer cells; Dendritic cells

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Core tip: This review covers the following core concepts of hepatitis B virus (HBV) persistence, according to the most up-to-date literature: Hepatocytes lack immune responsiveness to HBV; Innate immune cells display weak responses at the early stages of HBV infection; HBV impairs functions of innate immune cells and select signaling pathways to evade immune recognition and response.

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a global health concern, as about 257 million people worldwide are chronically infected with HBV currently^[1]. Although the HBV infection rate has been partly controlled by various prophylaxis strategies, researchers have yet to discover a cure for chronic HBV infection. Chronic hepatitis B (CHB) is typically asymptomatic, but harbors the potential for development of life-threatening complications^[2]. To overcome this threat, the mechanisms of HBV infection that underlie progression to chronicity need to first be fully elucidated.

HBV, a member of hepadnavirus family, acts as a "stealth" virus, not inducing any obvious innate immune responses in the early stage of infection^[3]. Furthermore, the target cells (hepatocytes) do not recognize HBV efficiently through known signaling pathways, indicating the possibility of an HBV immune evasion mechanism^[4]. HBV also has the ability to suppress functions of innate immune cells^[5-7]. HBV interaction with innate immunity would suggest that HBV persistence is related to a multitude of host and viral factors.

Herein, we summarize the recent knowledge regarding HBV persistence and the evidenced and theorized relations with intrahepatocyte signaling pathways and innate immune cells. Collation of such information will provide a useful overview of the field today, possibly providing new insights into novel therapeutic treatments for CHB.

Fundamentally, the innate immunity system responds to viral infection in three phases. In the first phase, various sensors in the cytoplasm recognize pathogen-associated molecular patterns, such as foreign DNA or RNA, and send a warning message to

initiate downstream signals. The second phase involves the proteins of the downstream signaling pathways transmitting the danger message to the nucleus, activating effector elements. In the last phase, the consequently up-regulated effectors [*i.e.*, inflammatory factors or interferon (IFN)-stimulating genes] degrade the exogenous viral elements. Defect or suppression of the involved sensors and signaling pathways tends to result in persistent existence of HBV in the host, since, under such circumstances, HBV cannot be recognized and eliminated in a timely manner. We will begin this review by discussing several intra-hepatocellular pathways that are closely related to HBV recognition and which exert an anti-HBV effect.

HEPATOCYTES LACK IMMUNE RESPONSIVENESS TO HBV

Pattern recognition receptors

Pattern recognition receptors (PRRs) are the major sensors of exogenous pathogens, and they include the Toll-like receptors (TLRs), retinoic acid-inducible gene I (*RIG-I*) and melanoma differentiation-associated gene 5 (*MAD5*)^[8]. These molecules are able to recognize diverse pathogen-associated common loci of specific pathogens, subsequently activating downstream signaling pathways that induce IFNs and inflammatory factors to control virus replication^[9]. However, a recent study of liver tissues from CHB patients found that hepatocytes do not respond to HBV, even though they were able to produce IFNs and induce expression of IFN-stimulating genes when stimulated by other infection-related factors, such as those related to TLR3 binding and Sendai virus infection. This finding suggested that HBV is invisible to PRRs on hepatocytes^[10].

Stimulator of IFN genes

Stimulator of IFN genes (*STING*) serves as the adaptor protein of multiple cytoplasmic DNA receptors that recognize exogenous pathogens^[11]. It has been reported that cytoplasmic DNA-activated cyclic GMP-AMP synthase (commonly known as cGAS) binds to *STING*, thereby inducing secretion of type I IFN and other cytokines^[12]. This pathway is of great importance for eukaryotes (eukaryotic cells) to defend against bacterial, viral and other eukaryotic pathogens^[11].

In vivo and *in vitro* experiments have shown that *STING* is NOT expressed in human hepatocytes, which might explain the dysfunction of DNA sensing^[4]. Hence, HBV DNA may have adapted to this particular "biological niche", whereby it can escape immune detection. More interestingly, c-GAMP is able to induce a robust cytokine response in a HBV-infected C3A^{hNTCP} hepatoma cell line if added in cell culture, suggesting its capacities of inhibiting HBV replication^[13].

INNATE IMMUNE CELLS HAVE WEAK RESPONSIVENESS TO HBV

Natural killer cells

Natural killer (NK) cells constitute 30%-40% of the intrahepatic lymphocytes, and are believed to play an indispensable role in HBV clearance. The NK cells exert their direct antiviral effects *via* secretion of IFN- γ , tumor necrosis factor (TNF)- α , granulocyte-macrophage stimulating factor, interleukin (IL)-10 and transforming growth factor- β to inhibit HBV replication or stimulate killing of infected cells^[14,15]. However, studies of the functions of NK cells in early HBV infection have produced controversial results.

In the woodchuck model of acute hepatitis B, NK cells are activated within 48-72 h after infection, consequently leading to a transient reduction of HBV replication; but, this activation is unable to induce a timely adaptive T cell response^[16]. Further, in chimpanzee models with self-limited HBV infection, NK cells do not become activated until the major histocompatibility complex-restricted α/β T cells enter the liver and recognize antigen; the T-specific cells, for the most part, carry out the clearance of HBV^[3]. Since these studies were carried out in animal models, it remains unclear to what extent the results mirror the human molecular processes.

In fact, the function of NK cells in early human HBV infection has proven very difficult to determine because the time frame from infection to diagnosis is typically more than 10-12 wk^[17]. Regardless of how the NK cells function in this process, T-specific cells are the primary cell-types responsible for HBV clearance. Thus, the inaction of NK cells, along with immature or coincidentally impaired functions of T cells, may explain how HBV infection progresses to chronicity.

In addition, in human CHB, immune responses of NK cells are known to be altered. These alterations include impaired cytolytic activity^[18] and up-regulation of antiviral T cell death receptors, the latter of which renders the cell susceptible to targeting for destruction by host mechanisms^[19]. Given that several studies have demonstrated that activated NK cells and T cells can cause liver damage^[20-23], the defective NK cells' functions and the NK cell-mediated disarming of T-specific cells might be protective for hepatocytes while simultaneously contributing to HBV persistence.

Kupffer cells

Kupffer cells (KCs) are macrophages residing in the liver sinusoids. Programmed to screen and clear pathogens that they engage, the KCs serve as scavengers. They produce pro- and anti-inflammatory cytokines, as well as other molecules known to have antipathogen activities. In the early phase of HBV infection, KCs directly interact with HBV and produce proinflammatory cytokines (*i.e.*, IL-6, TNF- α and IFN- α) to elicit their antiviral effects^[24,25]. Subsequently, NK cells and HBV-

specific immunity are also activated to aid in eradication of the virus. While the interaction between KCs and hepatitis B surface antigen (HBsAg) is mostly dependent upon the TLRs^[25,26], expression of TLR3 is found to be significantly decreased in CHB patients (compared to that in healthy controls); this aberrant expression may contribute to HBV chronicity.

Moreover, if HBV infection progresses to chronicity, the role of KCs will change, just as that of NK cells. The major cytokines secreted by KCs shift towards an anti-inflammatory profile (*i.e.*, increased IL-10, which is known to contribute to the persistent existence of HBV in the host). In virus-persistent mouse models, stimulation of TLR2 by the hepatitis B core antigen leads to up-regulation of IL-10 secretion by KCs, with the ultimate detrimental exhaustion of anti-HBV CD8⁺ T cells^[27]. IL-10 suppresses not only T cell-mediated specific immunity but also humoral immunity^[28]. As such, KC depletion or IL-10 deficiency will lead to restoration of CD8⁺ T cell function, breaking the cycle of humoral immune tolerance and allowing for clearance of the HBV^[29]. Thus, the collective results in the literature have revealed that KC secretes IL-10 in chronic HBV infection to disarm humoral and cellular immunity, which leads to HBV persistence.

Dendritic cells

Dendritic cells (DCs) represent the most efficient professional antigen-presenting cell type. As such, although they reside universally throughout the body, their frequency accounts for less than 1% of the total peripheral blood mononuclear cells. Classified by expression of specific surface markers, the DCs are divided into several types, with those most frequently studied in chronic HBV infection being the plasmacytoid (p)DCs and the myeloid (m)DCs.

Besides antigen processing and presenting, the pDCs produce appreciable amounts of IFN- α , which serves to inhibit viral replication *via* the TLR7/9 signaling pathways, when stimulated. However, some studies have demonstrated that the frequency of pDCs is reduced in CHB patients (as compared with normal controls)^[30-32], indicating that HBV persistence is associated with pDC reduction. This hypothesis, however, has been doubted following the finding of pDC frequency in CHB patients being similar to that in healthy individuals^[33-36]. Considering the rarity of pDCs in blood, it is likely that different experimental protocols account for the inconsistencies among these findings.

Regardless of the frequencies, the functions of pDCs are indeed hampered in chronic HBV infection. Most studies have reported a significant reduction of IFN- α secretion from pDCs^[6,30-34]. Notably, the level of IFN- α has been found to be negatively correlated with alanine aminotransferase levels^[33]. This finding could reflect a mechanism of HBV immune evasion and persistence, and an immune regulatory role for pDCs in this infection.

Nevertheless, findings from an exceptional study led the authors to argue that pDC function was not impaired in chronic HBV infection^[35]. The overall question remains unanswered.

mDCs are primarily responsible for inducing T cell differentiation and producing TNF- α . Unlike the pDCs, most studies on this cell type have found no difference in mDC frequency between CHB patients and healthy people^[34-36]. Similar to the pDCs, however, it has been observed that the capacity of TNF- α production is impaired in mDCs when stimulated by HBV^[34]. The other primary ability of mDCs, that of inducing T cell differentiation and proliferation, has not yet been defined in CHB patients.

HBV VIRUS-MEDIATED DISRUPTION OF THE HOST IMMUNOLOGICAL RESPONSE

RIG-I

HBV-induced type III IFN expression depends on RIG-I^[37]. A recent study has suggested that over-expressed RIG-I could dramatically reduce the levels of HBV mRNA and DNA *in vitro*^[9]. More interestingly, RIG-I can directly exert antiviral function by preventing the HBV P protein from binding with the HBV pregenomic RNA 5' stem-loop region^[37]. MAD5 and RIG-I can recognize many viral RNAs, subsequently initiating downstream signaling pathways by up-regulating the adapter protein mitochondria-antiviral signaling protein [MAVS, also known as virus-induced signaling adaptor (VISA) and interferon promoter stimulator-1 (IPS-1)]. In turn, the IFN regulatory transcription factor 3 (IRF3) and nuclear factor-kappa B (NF- κ B), two of the most important proinflammatory transcription factors, become activated^[38]. It has been reported, however, that the quantity of MDA5 is obviously decreased in CHB patients (compared to healthy controls)^[39]. Moreover, a recent study revealed that HBV-induced miR146a attenuated innate immunity through targeting of RIG-I and RIG-G^[40].

TLRs

In rat models, TLR3 activation has been shown to result in the production of type I IFN to control HBV replication^[41]. In mammalian cells, TLR2 and TLR4 share the MyD88-dependent signaling pathway, so that they mediate activation of the same downstream signaling pathways, including the NF- κ B, MAPK and PI-3k/Akt pathways. Ultimately, the production of proinflammatory cytokines (*i.e.*, TNF- α and IL-8) are up-regulated in hepatocytes, to inhibit the HBV replication^[42].

Intriguingly, lower expression of TLR2 has been observed in hepatocytes, KCs and peripheral monocytes of hepatitis B e antigen (HBeAg)-positive CHB patients (compared with that in HBeAg-negative CHB and controls)^[43]. Further research found that this down-regulated expression correlated with the levels of plasma

HBsAg^[44] and that HBsAg was able to selectively inhibit TLR2-induced IL-12 production from human monocytes/macrophages in a dose-dependent manner^[45]. HBeAg was also shown to specifically inhibit the TLR-mediated activation of NF- κ B and IFN- β ^[46].

MAVS

MAVS is a downstream signaling pathway protein of RIG-I and MAD5. Localized in mitochondria^[47], mitochondria-associated endoplasmic reticular membranes^[48] and peroxisomes^[49], the protein contains an N-terminal CARD-like domain and a C-terminal transmembrane domain, anchoring to the mitochondrial membrane^[47]. RIG-I and MAD5 detect exogenous RNA in lymphocytes, subsequently communicating with the mitochondrial membrane and interacting with MAVS. Consequently, NF- κ B and IRF3 become activated and induce IFN. Thus, MAVS is regarded as the central hub of the RIG-IFN axis.

In the absence of MAVS, cells do not produce type I or III IFN or proinflammatory cytokines upon infection with RNA virus^[47]. This result was recapitulated in MAVS knockout mice^[50]. In addition, the HBV X protein mediates the degradation of MAVS by utilizing Lys(136) ubiquitin (directly on the MAVS protein), thereby suppressing the induction of IFN- γ ^[51] (Figure 1).

HBV-MEDIATED DYSFUNCTION OF INNATE IMMUNE CELLS

HBV alters NK cell function

A study group found that the pDC-NK cell crosstalk was suppressed by HBV^[5], which might explain why the reaction of NK cells in early HBV infection is dull. Activation of NK cells is strongly dependent on IFN- α produced by pDCs^[52]. HBsAg and HBeAg were also found to impair NK cell function, through the down-regulation of IFN- γ expression^[7,53]. In CHB patients, IFN- γ production is declined, and restoration of the IFN- γ -producing capacity is achievable after viral load reduction^[54]. Consequently, the antiviral capacity of NK cells is compromised in chronic HBV infection^[55-58]. In addition, HBV can stimulate generation of suppressive monocytes to initiate regulatory NK cell differentiation, resulting in T cell inhibition^[59].

HBV suppresses the function of TLRs in KCs

As mentioned above, KCs' ability to combat HBV infection mainly depends on expression of TLRs, but HBV itself can develop the ability to suppress TLR-mediated innate immune responses in the liver^[26,60]. Accordingly, HBV replication will be controlled when TLRs are stimulated by agonists; the effective TLRs that potentially inhibit HBV replication have been identified as TLR3 and TLR4^[41]. In addition, the expression of TLR3 displays restoration after antiviral therapy^[61] and hepatic HBV infection triggers a TLR3-dependent immune responses in the absence of HBsAg^[62]. Thus, HBsAg

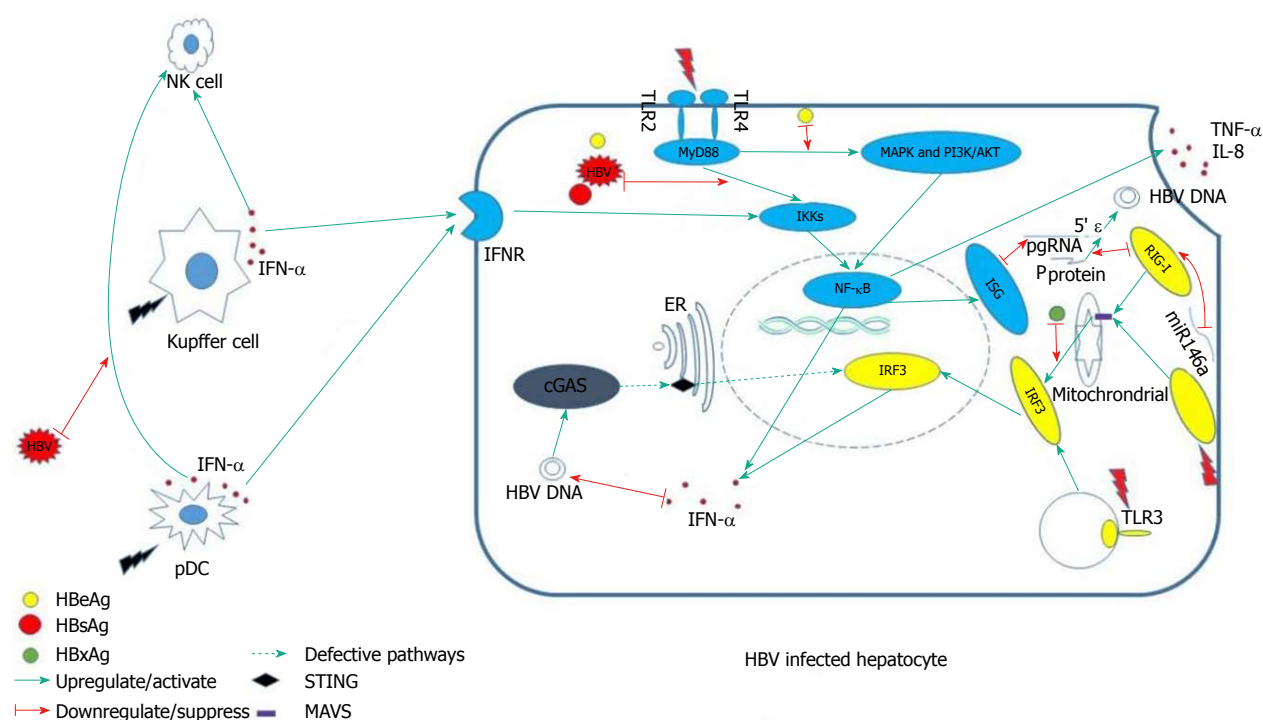


Figure 1 Relationships between hepatitis B virus and innate immunity system. NK cell: Nature killer cell; IFN- α : Interferon- α ; IFNR: Interferon receptor; HBV: Hepatitis B virus; cGAS: Cyclic GMP-AMP synthase; TLRs: Toll-like receptors; pDC: Plasmacytoid dendritic cells; MyD88: Myeloid differentiation primary response 88; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol-3 kinase; NF- κ B: Nuclear factor-kappa B; IRF3: IFN regulatory transcription factor 3; ER: Endoplasmic reticulum; TNF- α : Tumor necrosis factor alpha; IL8: Interleukin 8; RIG1: Retinoic acid-inducible gene 1.

might be at the center of the yet-to-be-defined HBV evasion mechanism.

HBV hampers secretion of antiviral cytokines from DCs

HBV lacks the capacity to activate pDCs, and many studies have also revealed that HBV could be able to inhibit IFN- α secretion from these cells^[6,30-34]. Similarly, HBV can also reduce TNF- α production by mDCs^[34]. Thus, HBV-mediated impairment of functions of both pDCs and mDCs suggests a potential mechanism of HBV persistence; but, the mechanism by which HBV induces such dysfunction remains elusive.

NOVEL THERAPEUTIC STRATEGIES THAT BOOST INNATE IMMUNITY

Currently, the most frequently applied strategy of CHB treatment is PEG-IFN- α /nucleoside analogs (NA) combination which works quite well. However, if altered NK cell functions are corrected, the outcome of the drug combination could possibly be improved. As described above, the functions and number of innate immune cells such as NK cells, KCs and DCs can be impaired in chronic HBV infection. Thus, replacing, restoring or boosting the functions of innate immune cells can be potential therapeutic targets for viral load reduction and further, HBV clearance. And in return, once viral load

reduction is achieved, the antiviral capacities of innate immune cells often restore.

IFN- γ is able to inhibit the HBV replication within hepatocytes in the absence of immune cells^[63]. Given that IFN- γ -producing capacity of NK cells restores after viral load reduction, it seems to be a positive-feedback when IFN- γ is used in HBV infection. What's more, compared with IFN- α , IFN- γ serves as efficient as IFN- α but causes less side effects^[64]. However, how IFN- γ combat HBV independent from immune cells remains unclear.

Agents enhancing the recognition of HBV could be used to wipe out HBV in the early stages of infection. Some known PRR agonists and TLR agonists could trigger a series of reaction in infected hepatocytes via IRF or NF- κ B pathways; since PRRs and TLRs are abundantly expressed in innate immune cells, such agonists are capable of rendering immune cells more powerful in recognizing HBV, thus contributing to early HBV clearance^[65,66]. Vesatolimod (GS-9620), an oral TLR7 agonist, which was already involved in the 2nd phase clinical trial, was surprisingly found to be able to cause dose-dependent pharmacodynamic induction of ISG15 and a significant increase of serum cytokines^[67].

Stimulation of certain innate immune cells to produce direct antiviral cytokines is another theoretical way to fight against human CHB. But in CHB patients,

Table 1 Cytokines and factors implicated in causing inflammation in atherosclerosis

Cytokines/factors	Abbreviations
Hepatitis B virus	HBV
Chronic hepatitis B	CHB
Interferon	IFN
Pattern recognition receptors	PRRs
Toll-like receptors	TLRs
Melanoma differentiation-associated gene 5	MAD5
Retinoic acid-inducible gene I	RIG I
Stimulator of IFN genes	STING
Cyclic GMP-AMP synthase	cGAS
Human sodium taurocholate cotransporting polypeptide	hNTCP
Natural killer cell	NK cell
Tumor necrosis factor	TNF
Interleukin	IL
Kupffer cells	KCs
Dendritic cells	DCs
Plasmacytoid dendritic cells	pDC
Myeloid dendritic cells	mDC
Mitochondria-antiviral signaling protein	MAVS
Virus-induced signaling adaptor	VISA
Nucleoside analogs	NA

there is a balance between antiviral activity and anti-inflammatory activity. It is unknown whether the agents would break the balance and what consequences they would bring (Table 1).

CONCLUSION

The crosstalk between innate immunity and HBV persistence has been a controversial topic for a number of years. The collective findings we present in this review demonstrate that HBV is able to hamper innate immunity in many ways, and even to alter the functions of innate immune cells in order to suppress specific immune responses. This partly explains why HBV manages to progress to chronicity and to exist persistently. We hope the field will build upon these insights, leading to a deeper and more comprehensive understanding of HBV persistence and the role of innate immunity. Such knowledge will serve as a foundation for future development of effective immunomodulation treatment for chronic HBV infection. Indeed, therapeutic strategies that aim to restore innate immune responses may represent remarkably potent tools for reducing HBV chronicity and, further, for eradicating HBV infection.

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