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TOPIC HIGHLIGHT

2016 Hepatitis B Virus: Global view

Innate immune targets of hepatitis B virus infection

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Abstract

Approximately 400 million people are chronically infected with hepatitis B virus (HBV) globally despite the widespread immunization of HBV vaccine and the development of antiviral therapies. The immunopathogenesis of HBV infection is initiated and driven by complexed interactions between the host immune system and the virus. Host immune responses to viral particles and proteins are regarded as the main determinants of viral clearance or persistent infection and hepatocyte injury. Innate immune system is the first defending line of host preventing from virus invasion. It is acknowledged that HBV has developed active tactics to escape innate immune recognition or actively interfere with innate immune signaling pathways and induce immunosuppression, which favor their replication. HBV reduces the expression of pattern-recognition receptors in the innate immune cells in humans. Also, HBV may interrupt different parts of antiviral signaling pathways, leading to the reduced production of antiviral cytokines such as interferons that contribute to HBV immunopathogenesis. A full comprehension of the mechanisms as to how HBV inactivates various elements of the innate immune response to initiate and maintain a persistent infection can be helpful in designing new immunotherapeutic methods for preventing and eradicating the virus. In this review, we aimed to summarize different branches the innate immune targeted by HBV infection. The review paper provides evidence that multiple components of immune responses should be activated in combination with antiviral therapy to disrupt the tolerance to HBV for eliminating HBV infection.

Key words: Hepatitis B virus; Infection; Targets; Innate immune response; Signaling pathway

Core tip: The pathogenesis of hepatitis B virus (HBV) infection is initiated and driven by complicated interplays between the virus and the host immune system. HBV DNA and different HBV proteins have various effects on different arms of innate immune system. The extent of HBV replication as well as the amounts of circulating

HBV antigens and different source of HBV proteins have heterogenous effects on innate immune responses and antiviral signaling pathways. Other factors, such as liver inflammation may also have impact on innate immune response. Multiple components of immune responses should be activated in combination with antiviral therapy to disrupt the tolerance to HBV for eliminating HBV infection.

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INTRODUCTION

Though hepatitis B virus (HBV) vaccine has been available for several decades and much progress has been made on anti-HBV therapeutics, there are still more than 350 million people chronically infected with HBV worldwide. The immunopathogenesis of HBV infection is initiated and propelled by complicated interactions between the host immune system and the virus[1].

It is recognized that host immune responses to HBV antigens are the major determinants of HBV pathogenesis and hepatocytes damage in the liver. On the contrary, viruses also exert immune regulatory effects to favor their replication. HBV has evolved active tactics to escape innate immune recognition and induce immunosuppression[2]. This has been displayed through the fact that HBV particles and proteins can be detectable around 5 wk postinfection, after which viral loads reach a logarithmic amplification stage[3]. The reason of the lag of viral replication is that the virus manages to evade being sensed by the innate immune system in the early phase of infection when the adaptive immune system has not been fully activated. HBV genome is 3.2 kbp in length and contains four overlapping genes that encode for the nucleocapsid (precore and core), polymerase, envelope (pre S and S), and hepatitis X proteins. The abundant HBV particles and viral proteins in the circulation in chronic HBV-infected patients allow multiple interactions among the virus, its viral proteins, and the immune system. HBV DNA and different HBV proteins have various effects on different parts of host immune systems, including immune cells and signaling pathways. The extent of HBV replication as well as the amounts of circulating HBV antigens, especially surface antigen (HBsAg), leads to heterogeneous profiles of the immune response, particularly in the context of chronic infection manifested as patients' different clinical profiles[4-6]. The immune tolerance phase has the highest level of serum HBsAg and hepatitis B e antigen (HBeAg) quantitation[7]. High levels of viremia, particularly high amounts of HBsAg, not only suppress innate immune cells, including monocytes, dendritic cells (DCs), natural killer (NK) cells, and NKT cells, through direct interaction, but also lead to exhaustion of cytotoxic T lymphocytes (CTLs) and helper T (Th) cells[8]. HBsAg mutations which enhanced the capability to avoid immune response were associated with HBV reactivation in a quite different clinical profiles[9]. Also, reduced viremia through antiviral therapy partially restores the impaired immune response[10] and the restored immune response status correlated with the levels of HBV infection parameters[11], which indirectly demonstrated the immune suppressive effect of HBV and its proteins.

A full understanding of the mechanisms as to how the virus inactivates various components of the immune system to maintain a persistent infection can help establish a new theory for designing novel immunotherapeutic methods and aid the eradication of the virus in chronic HBV infection.

Innate immune pathways are the targets of HBV to evade host antiviral responses contributing to chronicity of infection. The components of the innate immune system targeted by HBV include pattern-recognition receptors (PRRs), DCs, NKs, NKT cells, and antiviral signaling pathways[2]. In addition to directly regulating the innate immune response, HBV also modulates the innate immunity through alteration of the expression of microRNAs (miRNAs)[12].

PRRs

PRRs, including toll-like receptors (TLRs), retinoic acid-inducible gene Ⅰ (RIG-Ⅰ) - like receptors, and NOD-like receptors (NLRs), are crucial for sensing invading pathogens, initiating innate immune responses, restricting the spread of infection, and facilitating effective adaptive immune responses[13]. The early inhibition of the innate immune response by HBV is mainly through TLR-3 and RIG-Ⅰ/melanoma differentiation-associated gene 5 (MDA5) signaling pathways, which leads to decreased expression of several proinflammatory and antiviral cytokine genes[14]. In the setting of chronic HBV infection, reduced TLR expression and interference of PRRs signaling pathways lead to the impairment of host innate immune response.

TLRs

TLRs sense pathogen-associated molecule patterns (PAMPs), including nucleic acid sequences in degraded viral particles, and activate antiviral mechanisms, including intracellular antiviral pathways, production of antiviral effector interferons (IFNs) and proinflammatory cytokines, and initiation of adaptive immunity[15]. TLR signaling pathways are important parts of the innate immune response in HBV infection. It has been demonstrated that TLR ligands could suppress HBV replication[16]. Also, the activation of TLRs plays an important part in preventing intrauterine HBV transmission[17]. Accumulating evidence has consistently shown that the expression and function of TLRs in immune cells reduced during chronic HBV infection[18]. Expressions of TLR2 mRNA and protein were remarkably reduced in peripheral blood monocytes (PBMCs) derived from chronic hepatitis B (CHB) patients[19].

HBV virions or proteins such as HBsAg and HBeAg may reduce TLR expression and abrogate TLR-induced antiviral activity. The inhibitory mechanisms include suppressing IFN-β production and induction of IFN-stimulated genes (ISG) and transcription factors, such as IFN regulatory factor 3 (IRF3) and nuclear factor-kappa B (NF-κB)[20]. HBsAg, HBeAg, and HBV particles could inhibit the activation of nonparenchymal liver cells by TLR3 ligands[20]. Jiang *et al*[21] demonstrated that TLR-induced the expression of IFN-γ, ISGs, and proinflammatory cytokines in murine Kupffer cells (KCs) and liver sinusoidal endothelial cells (LSECs), and the activation of NF-κB, IRF3, and mitogen-activated protein kinases (MAPKs) in hepatocytes were strongly suppressed by HBsAg. TLR3-stimulated KCs and LSECs mediated T-cell activation was also suppressed by HBsAg. Visvanathan *et al*[22] first showed that TLR2 expression on liver cells, KCs, and PBMCs significantly reduced in HBeAg-positive CHB patients compared with HBeAg-negative CHB and controls. TLR2 detects several microbial PAMPs and subsequently activates NF-κB in a myeloid differentiation primary response gene 88 (MyD88)-dependent manner. Therefore, decreased TLR2 expression may lead to impairment of immune responses to HBV infection[23]. In addition to directly inhibits the TLR2-mediated c-Jun N-terminal kinase/MAPK pathway, HBsAg may also induce interleukin (IL)-10 production in monocytes indirectly[24,25]. Thus, TLR2 is an important immune target of HBV infection.

Toll/IL-1 receptor (TIR) domain-containing adapter protein inducing IFN-β (TRIF) is an important component in innate immune signaling pathways. It is one of the main intracellular adapter proteins required for TLR3 and TLR4 signaling. Ayoobi *et al*[26] suggested that the expression of TRIF significantly decreased in PBMCs isolated from CHB patients compared with those isolated from healthy subjects. TRIF protein was also downregulated in human hepatoma cell lines and liver tissue specimens infected with HBV[27]. HBeAg interacted with TRIF-related adaptor molecule (TRAM), Mal, and TLR2 at the subcellular level, and mutated HBeAg not only may disrupt the interaction between Mal and MyD88 but also ablate homotypic TIR:TIR interaction, which is crucial for TLR-mediated signaling[28]. Furthermore, HBeAg can suppress TIR and IL-1β-mediated activation of the inflammatory transcription factors, such as NF-κB and inhibit NF-κB and IFN-β promoter activity[29]. These results suggest the presence of intracellular precore protein in addition to secreted extracellular HBeAg.

Hepatitis B virus X (HBx) and polymerase (Pol) are the proteins that interfere with the PRRs pathways most frequently[2,30]. For instance, HBx reduced TRIF protein expression *via* the proteasomal pathway in a dose-dependent manner[31]. However, no direct convincing evidence indicating that HBV RNAs, DNAs and proteins are authenticly recognized by TLRs is available up to date. The interplay between HBV proteins and TLRs should be verified directly *in vivo* through further investigation[15].

RIG-Ⅰ - MDA5 pathway

MDA5 and RIG-1 as the PRRs play important roles in viral mRNA recognition. HBx and HBV Pol are involved most frequently in the inactivation of the RIG-Ⅰ pathways and ultimately impaired IFN production. HBx is a pivotally protein involved in HBV-associated liver diseases. Studies[32] indicate that HBx can interact with the mitochondrial membrane protein virus-induced signaling adapter (VISA), which is a key adapter protein downstream RIG-Ⅰ and MDA5, and interrupts the association of VISA with its upstream and downstream parts. This inhibits the induction of type Ⅰ IFNs through the activation of transcription factors, including NF-κB and RF3. Human cell line studies[33] have also suggested that adapter protein mitochondrial antiviral signaling (MAVS) is another target for HBx. The RIG-Ⅰ/MDA5 pathway and IFN-β induction is inhibited due to degradation of MAVS promoted by HBx. A recent study[34] showed that mRNA levels of MDA5 and RIG-Ⅰ dramatically decreased in CHB patients in comparison with healthy controls. However, these mRNA levels have little alteration among CHB patients with different states of HBeAg and HBV DNA viral loads. Moreover, RIG-Ⅰ could also offset the interaction of HBV Pol with the 5’-ε region, which suggest that RIG-Ⅰ dually actions as an HBV sensor activating innate signaling and counteracting viral Pol in human liver cells[35]. Therefore, the mechanism underlying the downregulation of MDA5 may attribute to several reasons in patients with CHB[34]. DDX3, an HBV Pol binding protein, belonging to the DEAD-box RNA helicase family, is associated with mRNA metabolism. HBV Pol blocks PRRs signaling *via* interaction with DDX3[36]. This may explain the mechanism of how HBV evading the innate immune response.

In contrast, Luangsay *et al*[14] found that the early inhibition of dsRNA-mediated response resulted from the HBV inoculum, but not HBsAg or HBeAg itself. Whereas, the significance of these results in the human needs to be confirmed.

DCs

DCs are key cells in the initiation of adaptive immune responses because of their ability of processing foreign antigens and presenting them to effector cells. Also, mature DCs can efficiently induce T-cell polarization to Th1 and generate HBcAg-specific CTLs[37]. A long-lasting debate exists on the functionality and phenotypes of DCs in chronic HBV infection. Several studies demonstrated that DCs functions were impairment in CHB patients, which included decreased expression of co-stimulatory molecules, defective cytokine production, and reduced allostimulatory capacity compared with healthy people[38,39].

However, Gehring *et al*[40] suggested that the frequency and function of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) were largely intact *ex vivo* in HBV infected patients except for the reduced IFN-α production compared with those of healthy donor DCs. They found that reduced IFN-α production did not correlate with viral titer, which suggested that viral antigens had slight impact on DCs function. The major confusion about the function of DCs resulted from studies which indicated that function of healthy donor DCs was impaired exposing to various sources of HBV *in vitro*, which are in contrast to the results obtained from CHB patients. Tavakoli *et al*[41] also demonstrated that phenotypes and functionality of circulating total DCs, mDCs, or pDCs are unaffected in chronically HBV infected patients whether experimented *ex vivo* or after *in vitro* activation and maturation. They demonstrated that isolated mDCs and pDCs from chronic HBV carriers showed the similar expression of co-stimulatory molecules and alloreactive T cell stimulation as that of the control DCs.

However, other studies showed that pDCs were the targets of HBV. Both HBV virions and purified HBsAg have immune modulatory functions and may directly contribute to the impairment of mDCs functions in chronic HBV infection[42]. HBV particles and HBsAg were capable of abrogating TLR9-induced *IFN-α* gene transcription *via* combining to TLR9-triggered pDC directly[43]. HBV not only directly interfered with pDC function, but also indirectly disturbed monocyte-pDC interaction. In addition, the ability of inducing the cytolytic activity of NK cells by TLR9-activated pDCs from CHB patients were also compromised[44]. Virus-like particles (VLPs) comprising small HBV envelope protein (HBsAgS) impaired IFN-α production of pDCs in response to CpG *in vitro*[45]. Op den Brouw *et al*[42] suggested that in the presence of HBV or HBsAg, cytokine-induced maturation resulted in a more tolerogenic mDC phenotype, as demonstrated by a significantly reduced upregulation of co-stimulatory molecules and a decreased T-cell stimulatory capacity, as demonstrated by T-cell proliferation and production of IFN-γ and IL-12. It has been shown that DCs from immune tolerant patients showed a prominently lower expression of CD80, CD86, and HLA-DR and demonstrated an injured stimulatory capacity in mixed lymphocyte reactions and decreased production of IL-12, compared with those in the inactive HBsAg carrier state. Also, no remarkable difference was observed between the indexes from inactive carrier and healthy controls[46]. Several studies[47,48] revealed that mDC frequency could return to the level of healthy donors, IL12p70 production increased, and lower expression of phenotypic molecules was restored with antiviral therapy of adefovir and lamivudine. These results indirectly demonstrated the suppressive effect of high loads of HBV particles and proteins on DCs.

Though with suppressive effect on DCs functions, HBsAg is also a component of HBV vaccine. HBsAg-pulsed DCs might promote HBV-specific immune response in CHB patients[49]. HBsAgS VLPs can deliver an antigen to both major histocompatibility complex (MHC)-Ⅰ and MHC-Ⅱ in primary DCs and facilitate cytotoxic and helper T-cell priming[45]. Also, Ag-Ab immune complexes could be easily captured and taken up by DCs[50], and could efficiently induce HBs-specific T cells. A clinical study showed that the immunity was enhanced by autologous HBsAg-activated DC-cytokine-induced killer cells as adoptive immunotherapy[51]. Martinet *et al*[52] showed that the vaccination of Hepato-HuPBL mice with the HBc/HBs peptide-loaded pDCs induced HBV-specific T cells with specific ability of lysing the transfected hepatocytes. In addition, HBeAg might have a negative effect on the generation of DCs from bone morrow precursors[53].

The mechanism underlying the suppressive influence of HBV and HBV proteins on the function of DCs has not been fully elucidated. Some reports indicated that HBV and HBsAg can enter the DCs and cause damage, leading to a decline in the number of DCs and functional impairment[45,54]. However, Tavakoli *et al*[41] found that viral mRNA was not detectable by reverse transcription-polymerase chain reaction in both DC populations, which argues against viral replication in DCs.

The arguments regarding the functions and phenotypes of DCs result from the heterogeneous source of HBV antigens, variability of patients, and assay methods of DC maturation and cytokine production *in vitro* across studies[40]. In addition, liver pathology also likely affects the function of pDCs. Studies show that IFN-α production by pDCs is negatively correlated with the serum alanine aminotransferase (ALT) level in patients with CHB[39,43]. Furthermore, the expression of inhibitory molecule programmed death-ligand 1 (PD-1) in mDCs tended to more closely relate to ALT level than to viral load[55].

NK AND NKT CELLS

NK cells, the main innate immune cells, play indispensable roles in the clearance of HBV from hepatocytes. Although the numbers, subset distribution, and cytotoxic capacity of NK cells were retained, their activation and IFN-γ and tumor necrosis factor (TNF)-α production, particularly of the CD56(dim) subset, were strongly hampered in patients with CHB compared with healthy controls[56]. NK cells express several kinds of stimulatory and inhibitory receptors, which interact with their respective ligands results in functional activation and suppression[57]. Activation status and surface receptor expression patterns of NK cells may be altered in HBV infection[2]. Natural killer group 2D (NKG2D) is a well-characterized activating receptor expressed on NK cells, NKT cells, and CD8(+) cytotoxic T cells, which binds to a diverse group of ligands that resemble the MHC-class Ⅰ molecules. Accumulating evidence has shown that NKG2D-ligand interactions play a crucial role in the persistence of HBV infection and the development of liver injury and hepatocellular carcinoma. The expression of NKG2D ligands may be modulated post-transcriptionally by HBV[1]. Also, high serum HBV DNA loads upregulate the expression of inhibitory receptors such as NKG2A, but downregulate activating receptors, CD16, NKp30, NKG2D, and NKp46[56,58,59]. One study showed that the expression of NKp46 negatively correlated with the HBV DNA level and was much higher in inactive HBsAg carriers compared with active infection patients. NKp46 activation may restore NK cell cytolytic activity to HepG2 and HepG2.215 cell lines *in vitro*[59]. Furthermore, NK cell phenotype and functionality may partially be restored by viral load reduction through antiviral therapy, as shown by downregulated expression of NKG2A and improved IFN-γ production as a result of an increased ability of CD56(dim) NK cells[56]. And the recovered function of NK cells was strongly associated with HBsAg clearance[60]. Under the combination treatment of pegylated IFN-α-2a and adefovir, compared with nonresponders, responders had a remarkably lower expression of NKG2A on CD56(dim) NK cells and higher CD56 (bright) TNF-related apoptosis-inducing ligand expression and IFN-γ production at the end of the treatment. These results were not observed in HBeAg-positive patients who developed HBeAg seroconversion without HBsAg clearance[60]. The spontaneous reduction of HBV loads had similar results[61].

In addition, HBeAg may inhibit IFN-γ production by NK cells mediated by IL-18 in a dose-dependent manner[62]. HBV may specifically suppress pDC-induced IFN-γ production by NK cells without affecting their cytolytic ability through pDC-NK cell cross-talk[63]. Although NK cell IFN-γ production was impaired in response to TLR9 stimulation in CHB patients compared with controls, the upregulation of CD69 expression in response to TLR9 was maintained[64].

NKT cells are a unique subgroup of T-cells expressing both NK cell surface marker-CD56 and a T-cell receptor CD3 - which are stimulated by lipid antigens. NK and NKT are the two cell types that are promptly activated in the early phase of HBV infection, which probably contribute to controlling the HBV invasion and allowing timely induction of adaptive immune responses[65]. While, it has demonstrated that the frequency of hepatic NKT cells from HBV transgenic mice was low and the capability of producing IFN-γ was impaired[66]. Reports by Jiang *et al*[67] and Zhu *et al*[68] indicated that the frequency of peripheral invariant NKT (iNKT) cells is lower in patients with chronic HBV infection than in healthy subjects, and returns to normal levels during viral control with telbivudine. In patients treated with PEG-IFN-α, the ratio of peripheral blood NKT cells in T lymphocytes before, during, and after treatment significantly elevated in the significant-effect group compared with the effect and no-effect groups[69]. This implies that NKT cells modulate the innate immune response against HBV infection and play a major role in effective antiviral treatment.

The mechanism underlying the decrease in the number and function of circulating iNKT cells in patients with CHB remains unclear. It is believed that this reduction is at least partially due to trafficking to the liver[70] because iNKT cells express a high level of CC chemokine receptor 5 (CCR5) and CCR6[67] which enable iNKT cells migrate toward the liver. Other mechanism may involved in the high expression of inhibitory molecules PD-1 and Tim-3, and lower the expression of CD28[66,71]. In addition, HBV-induced lipid alterations also contributed to a change in NKT cell function[72].

IMMUNE TARGET OF SIGNALING PATHWAYS OF THE ANTIVIRAL RESPONSE AND CYTOKINES

Recognition of viral infections by PRRs, such as TLRs and RIG- I /MDA5, activates signaling pathways and leads to the induction of inflammatory and antiviral cytokines, such as type I IFN, that limit viral replication and initiation of adaptive immunity. The expression of TLR signaling molecules, such as MyD88, IL-1 receptor-associated kinase 1 (IRAK1), and IRAK4, significantly decreased in PBMCs from CHB patients compared with healthy controls[73,74].

HBV proteins, such as HBV Pol and HBx, could interfere with multiple sites of intracellular signaling pathways triggered by HBV infection, preventing IFN production and antiviral responses in hepatocytes[30,75]. HBV Pol can inhibit TANK-binding kinase 1 (TBK1)/IkappaB kinase-epsilon (IKKi), the effector kinases of IRF signaling. It can block IRF signaling activation mediated by TLR-3 or RIG- I recognizing dsRNA in the endosomes or in the cytosol through interaction with DDX3, a transcriptional factor of the IFN-β promoter in human hepatoma cell lines[30,32,36]. HBV Pol mediates blockage of IFN-α signaling through suppressing IFN-α-induced signal transducers and activators of transcription 1 (STAT1) serine 727 phosphorylation and STAT1/2 nuclear accumulation[76]. Pol also affects STAT methylation through increasing protein phosphatase 2A (PP2A) expression, which inhibits protein arginine methyltransferase 1, the enzyme that catalyzes the methylation of STAT1[77]. This may be responsible for HBV resistance to PEG-IFN-α therapy[78]. However, HBV Pol does not interfere with STAT1 degradation and phosphorylation[79]. The cytosolic DNA sensor and key adaptor stimulator of *IFN* genes (STING) has been suggested to be critical in multiple foreign DNA-elicited innate immune signaling. Screening analysis demonstrated that the reverse transcriptase and the RNase H (RH) domains of HBV Pol were responsible for the inhibition of STING-stimulated IRF3 activation and IFN-β induction[80]. One study has demonstrated that HBV Pol preferentially suppresses TNF-α-, TLR3- or TLR4-induced NF-κB signaling by inhibiting the activity of IKK complex through disrupting the association of IKK/NF-κB essential modulator (NEMO) with Cdc37/Hsp90β in hepatoma cells[81]. Therefore, in addition to its inherent catalytic function, HBV Pol has multifunctional immunomodulatory effects. It may counteract the innate

Table 1 Innate immune cells, molecules and signaling pathways targeted by hepatitis B virus and hepatitis B virus proteins

HBV and HBV proteins	Innate immune cells, molecules and signaling pathways	Ref.
HBs	TLR, ISG, IRF3, IFN-β and NF-κB	[20]
	KCs, LSECs, IFN-γ, ISGs, MAPKs, TLR3	[21]
	JNK/MAPK, κBα	[24,25,87]
	mDCs, pDCs, TLR-9	[42,43]
HBe	Hepatocytes, KCs, PBMCs, and TLR2, ISG, IRF3, IFN-β and NF-κB	[20,22]
	TRAM, Mal, TLR2, and TIR:TIR	[28]
	NF-κB and IFN-β promoter, IFN-γ	[29,62]
	RIPK2	[83]
HBx	TRIF, RIG-I/MDA5, VISA, MAVS, NF-κB	[31-33,82]
	NEMO, TBK1, IKKi, and IRF3	[75]
HBV Pol	RIG-I, DDX3, NEMO-Cdc37/Hsp90β	[35,36,81]
	TBK1/IKKi, STAT1, PP2A, STING	[32,33,36,76,77,80]
HBV	NK, NKG2D, NKG2A, CD16, NKp30, and NKp46	[56,58,59]
	pDC-NK, NKT	[63,72]
	CTHRC1	[84]

HBs: Hepatitis B surface antigen; HBe: Hepatitis B e antigen; HBx: Hepatitis B x protein; HBV Pol: Hepatitis B polymerase; TLRs: Toll-like receptors; ISG: Interferon-stimulated genes; IFN: Interferon; NF-κB: Nuclear factor κB; KCs: Kupffer cells; LSECs: Liver sinusoidal endothelial cells; MAPKs: Mitogen-activated protein kinases; JNK: c-Jun N-terminal kinase; mDCs: Myeloid dendritic cells; pDCs: Plasmacytoid DCs; PBMCs: Periperal blood mononuclear cells; TRAM: TRIF-related adaptor molecule; TIR: Toll/interleukine-1 receptor; RIPK2: Receptor-interacting serine/threonine protein kinase 2; TRIF: TIR domain-containing adapter protein inducing IFN-β; RIG-Ⅰ: Retinoic acid inducible gene Ⅰ; IRF: Interferon-regulatory factors; MDA5: Melanoma differentiation associated gene 5; VISA: Virus-induced signaling adapter; MAVS: Mitochondrial antiviral signaling; TBK1: TANK-binding kinase 1; IKKi: KappaB kinase-epsilon; STAT1: Signal transducers and activators of transcription 1; PP2A: Protein phosphatase 2A; STING: Stimulator of IFN genes; NK: Natural killer; NKG2D: NK group 2D; NKG2A: NK group 2A; NKT: NK Tcell; CTHRC1: Collagen triple helix repeat containing 1; HBV: Hepatitis B virus; MAPK: Mitogen-activated protein kinase; NEMO: NF-κB essential modulator.

responses at different steps.

Similar to HBV Pol, HBx can target multiple points of signaling pathways negatively regulating type Ⅰ IFN production. In addition to RIG-Ⅰ, TNF receptor-associated factor 3, and TRIF, HBx also interacts with NEMO, TBK1, kinase-epsilon (IKKi), and IRF3[75]. HBx can also transactivate multiple transcription factors including NF-κB that regulates inflammatory-related genes. A recent report has suggested that HBx-evolutionarily conserved signaling intermediate in toll pathways interaction plays an important role in in IL-1β induction of NF-κB activation[82].

In addition to HBV Pol and HBx proteins, HBeAg may also modulate the intracellular signaling pathways. HBeAg may target receptor-interacting serine/threonine protein kinase 2 through inhibiting its expression and interacting with it[83] which may results in inactivation of NF-κB. Experiments indicate that collagen triple helix repeat containing 1 (CTHRC1) expressed in HBV-transfected cells facilitates HBV replication in cultured cells and BALB/c mice. On the other hand, HBV increases CTHRC1 expression, which downregulates the activity of type Ⅰ IFN, the transcription of ISGs, and the phosphorylation of STAT1/2[84].

However, some of the signaling pathways are important in restraining HBV replication. Tzeng *et al*[85] demonstrated that not IFN-α/β receptor, RIG-Ⅰ, MDA5, MyD88, NLR pyrin containing 3, caspase recruitment domain, and IL-1R but TNF-α is essential for HBV eradication. In the absence of TNF-α, or early treatment with the soluble blocker of TNF receptor in mice leads to HBV persistence[86]. This may explain the mechanism of HBV reactivation during TNF blockage agents therapy.

In contrast to HBeAg, research has reported that the treatment of human monocyte-derived DCs with HBsAg resulted in enhanced cell surface expression of CD80, CD83, CD86, and MHC-Ⅱ, and increased IL-12 p40, IL-12p70, and IL-10 production through decreasing inhibition of κBα concentrations and MAPK phosphorylation[87].

CONCLUSION

The suppression of various innate immune components targeted by HBV and HBV proteins may result in virus spread and subsequent inefficient adaptive immune responses, leading to HBV persistence. However, still controversies exist regarding the effects of HBV on the functionalities and phenotypes of innate immune cells, especially DCs. The conflicting results may be due to patient diversity, divergence of antigen sources, and inconsistent assay methods. Some of the findings derived from cell line and animal models remain to be defined for the human HBV infection. Furthermore, the knowledge of the exact mechanism of action of HBV and HBV proteins on some of the sites of the complicated innate signaling pathways is lacking. The updated findings of innate immune cells, molecules and signaling pathways targeted by HBV and HBV proteins are summarized in Table 1. The present study provides evidence that multiple components of immune responses should be activated in combination with antiviral therapy to disrupt the tolerance to HBV for eliminating HBV infection.

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