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TOPIC HIGHLIGHT

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Immunopathogenesis of chronic hepatitis B

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Abstract

Chronic hepatitis B (CHB) is a widespread infectious disease with unfavorable outcomes and life-threatening consequences for patients, in spite of modern vaccination and antiviral treatment modalities. Cutting-edge experimental approaches have demonstrated key pathways that involve cross-talk between viral particles and host immune cells. All events, including penetration of hepatitis B virus (HBV) particles into host cells, establishing persistence, and chronization of CHB infection, and possibility of complete elimination of HBV particles are controlled by the immune system. Researchers have paid special attention to the replication capacity of HBV in host cells, which is associated with cellular changes that reflect presentation of viral antigens and variability of HBV antigen features. In addition, specific HBV proteins have an immune-modulating ability to initiate molecular mechanisms that "avoid" control by the immune system. The relationship between immunological shifts and chronic infection stages has been intensively studied since it was recognized that the immune system is a direct participant in the recurrent (cyclic) nature of CHB. Understanding the wide diversity of molecular pathways and the crosstalk between innate and adaptive immune system components will provide fresh insight into CHB immune pathogenesis and the possibilities of developing new treatment strategies for this disease.

Key words: Chronic hepatitis B; Immunopathogenesis;

Immune response; Hepatocellular carcinoma; Antiviral drugs

Core tip: Chronic hepatitis B (CHB) immunopathogenesis has been comprehensively studied worldwide. Current evidence on the molecular pathways, crosstalk between viral particles and host cells, the role of viral proteins in triggering immune responses, and the content of recruited cells during different stages of viral infection is reviewed aimed at comprehensive analysis and systematization. Concepts concerning the interactions of immune cells in persistent CHB infection have changed, reflecting the possibility of designing new treatment strategies for this disease based on personalized approaches, molecular pathways, and evidence-based criteria.

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INTRODUCTION

Despite significant progress made in vaccination and antiviral therapy, viral hepatitis B still remains one of the most serious problems in medicine. As of now, 350-400 million people worldwide are chronically infected with hepatitis B virus (HBV). The prevalence of HBV-infection in various countries ranges from 0.1% to 20%[1,2], and annually about 1 million people die from HBV-associated diseases[3]. About 10%-30% of patients with chronic HBV infection are at increased risk of developing a progressive liver disease, coupled with fibrosis and cirrhosis[4-7]. One out of every four patients with cirrhosis due to HBV infection suffers from decompensation of liver function within 5 years, and 5%-10% of the patients develop hepatocellular carcinoma. Nearly 15% of patients with cirrhosis of liver succumb to death within 5 years, if untreated[8,9].

Chronic inflammatory and fibrous changes in the liver during HBV infection, as well as oncogenesis in the case of chronic hepatitis B, are by and large propelled by complex interactions between the virus and the host immune system[10]. Although extensive clinical and experimental research has helped improve diagnostic assessment, prevention and treatment of hepatitis B, a better understanding of the interplay between the host immune response and the virus may lead to the discovery of new immunotherapeutic and antiviral approaches to control persistent HBV infection. The focus of this review is to discuss previous accomplishments and studies on the effects of HBV proteins and innate and adaptive immune response of the host against the development of chronic hepatitis B (CHB).

HEPATITIS B VIRUS: STRUCTURE AND REPLICATION

Hepatitis B virus (HBV) is a hepatotropic DNA-containing virus of the Hepadnaviridae family. It is able to cause acute and chronic liver infections and is unique in many respects.

The HBV genome is represented by a partially double-stranded, relaxed-circular DNA (RC-DNA) molecule, which is surrounded by a lipid bilayer studded with viral glycoprotein complexes[11]. The external minus strand is 15%-45% longer than the internal plus strand and has a protein covalently linked to its 5' end-the viral polymerase[12]. The plus strand has a short capped RNA appended to its 5' end[13]. HBV DNA molecules are enclosed in a capsid protein with an antigenic structure designated as hepatitis B virus core antigen (HBcAg), and precore protein termed hepatitis B e antigen (HBeAg). On the exterior are envelope proteins-hepatitis B surface antigen (HBsAg) (S), preS1 (M), and preS2 (L)[11].

Early events in the HBV life cycle in the hepatocyte, including entry, uncoating, and delivery of the viral genome into the nucleus are not well understood. The details of the replication cycle are shown in Figure 1. Upon infection, the viral nucleocapsid moves into the cell and enters the nucleus exemplified by an *in vitro* model for the nuclear transport of the hepadnavirus genome[14]. In the nucleus, the viral RC-DNA is converted into double-stranded, covalently closed circular DNA (cccDNA). The cccDNA serves as the template for transcription of four polyA-tailed viral mRNAs with lengths of 3.5, 2.4, 2.1 and 0.7 kb[15]. These RNAs are transported to the cytoplasm where translation provides the viral nucleocapsid and precore antigen C (C, pre-C), polymerase (P), envelope large (L), medium (M), small (S), and transcriptional transactivating proteins (X). The 3.5 kb RNA molecule longer than the genome itself (pregenomic RNA, or pgRNA) is enveloped into the core particles along with the polymerase[16].

The pgRNA inside the particles serves as template for the reverse transcription of viral genome[17]. The newly formed polymerase/reverse transcriptase binds to the 5' end of pgRNA template. First, the minus strand is formed by reverse transcription of pgRNA which in turn serves as a template for the synthesis of plus strand. Once partially double-stranded DNA has been generated, nucleocapsids can go through a maturation event that enables the acquisition of an outer envelope *via* budding into the lumen of endoplasmic reticulum (ER)[15]. These nucleocapsids also can travel to the nucleus to enhance the copy number of cccDNA[11,18].

In the course of viral replication, α-taxilin has been shown to have a crucial role in the release of HBV particles[19]. The envelope surface polypeptides L, M and S are synthesized in excess (conventionally known as "HBsAg") and are most frequently identified in the blood of HBV-infected persons[20]. The functions of supplemen-

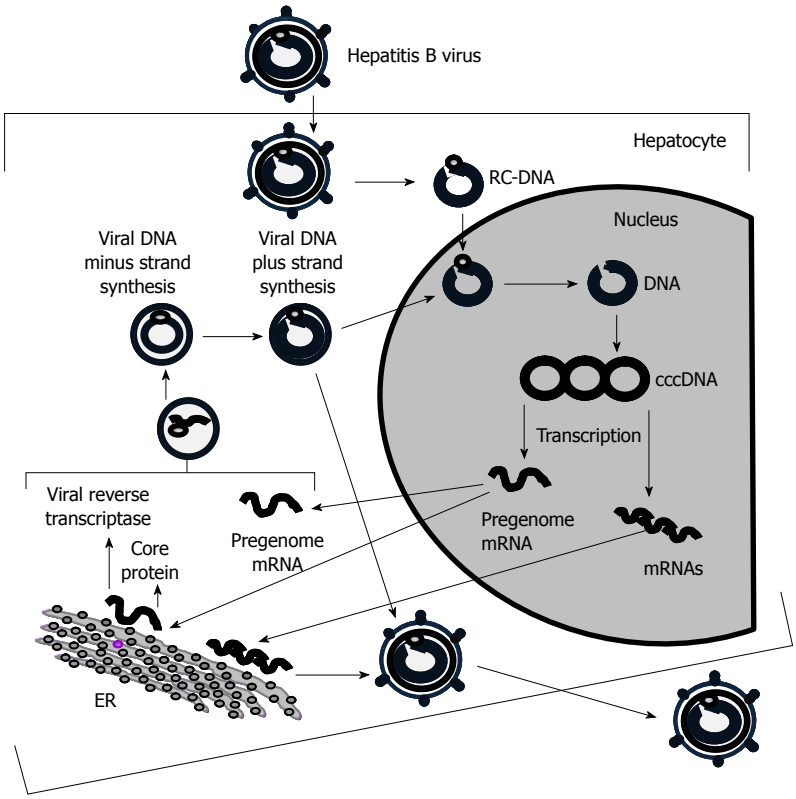

Figure 1 Hepatitis B virus DNA replication. Hepatitis B virus (HBV) penetration inside a hepatocyte occurs *via* interaction of envelope proteins with the cell receptors. Viral DNA release from the nucleocapsid with the help of the cellular enzymes takes place in the cytoplasm. After that the viral DNA gets into the nucleus and forms a circular structure-covalently closed circular DNA (cccDNA) which by transcription contributes to the formation of pregenomic RNA and three more mRNAs. Pregenomic RNA leaves the nucleus, gets into endoplasmic reticulum (ER) and serves as a template for synthesis of the core protein and the viral reverse transcriptase. The newly synthesized proteins in combination with free molecules of pregenomic RNA form the nucleocapsid. In the nucleocapsid with help of the reverse transcriptase and the pregenomic RNA as template, the minus strand is synthesized, which later serves as a template for the formation of the plus strand. The formed virus nucleocapsid can either take part in amplification of the viral genome or reach the ER and associate with precore protein and envelope proteins coded by other (non-pregenomic) mRNAs to form a mature virion, then leave the hepatocyte.

tary HBV genic products, e antigen (HBeAg) and viral X-protein (HBxP), are closely linked with hepatitis B pathogenesis and its outcome. HBeAg is an end product of translation of the 3.5 kb mRNA[20]. Detection of this antigen in the circulation of HBV-infected persons is known to be a substitute marker of high-level viral replication[20]. The presence or absence of the above antigen in the blood makes it possible to distinguish between HBeAg-positive and HBeAg-negative variants in the course of chronic hepatitis B[21]. HBeAg-positive variant is characterized by a more severe course, with unpredictable spontaneous outbursts of hepatic inflammation that quickly progress to hepatic fibrosis[22].

Close and distinct functional interconnection of HBV replication with the host gives rise to a high HBV variability. Indeed, the HBV genome exhibits nucleotide divergence, from which it is possible to distinguish eight main genotypes (A-H), with a different geographic prevalence. An interrelationship apparently exists between HBV genotype and clinical manifestations, as well as effectiveness of antiviral therapy[23,24].

Domingo *et al*[25] viewed cccDNA as the main object of mutation, giving rise to genotype variants in HBV. Sequences that were dominant at an earlier phase of evolution of the same HBV lineage can be reintroduced in the pool of actively replicating HBV[16]. HBV cccDNA is responsible for occult HBV infection in patients with low or negative HBsAg and HbeAb, and who may have a low or undetectable level of HBV DNA in serum[26]. Persistence of HBV DNA, and possibly its integration into cellular DNA, might play a role in the development of hepatocellular carcinoma (HCC)[27]. Selection of different HBV variants is affected by multiple factors in addition to viral and host factors, such as antiviral treatment (nucleoside and nucleotide analogues), HBIg intervention, vaccination, and the lack of proofreading by the viral reverse transcriptase[25,28].

HBV does not have a direct cytopathic effect on the liver cell[10,29]. Typically, the death of hepatocytes in CHB is a result of apoptosis. HBV by itself, as well as some of its proteins (HBxP and HBsAg), were reported to induce hepatocyte apoptosis, in particular, by the TRAIL-mediated mechanism[30], bringing the number of perishing cells to a clinically significant level[31]. Damage to hepatic tissue results from the immune reaction against viral antigens and the activation of cytotoxic T cells ($CD8^+$, CTL)[32]. It was verified that there is no cause-and-effect relationship between the extent of hepatocyte damage

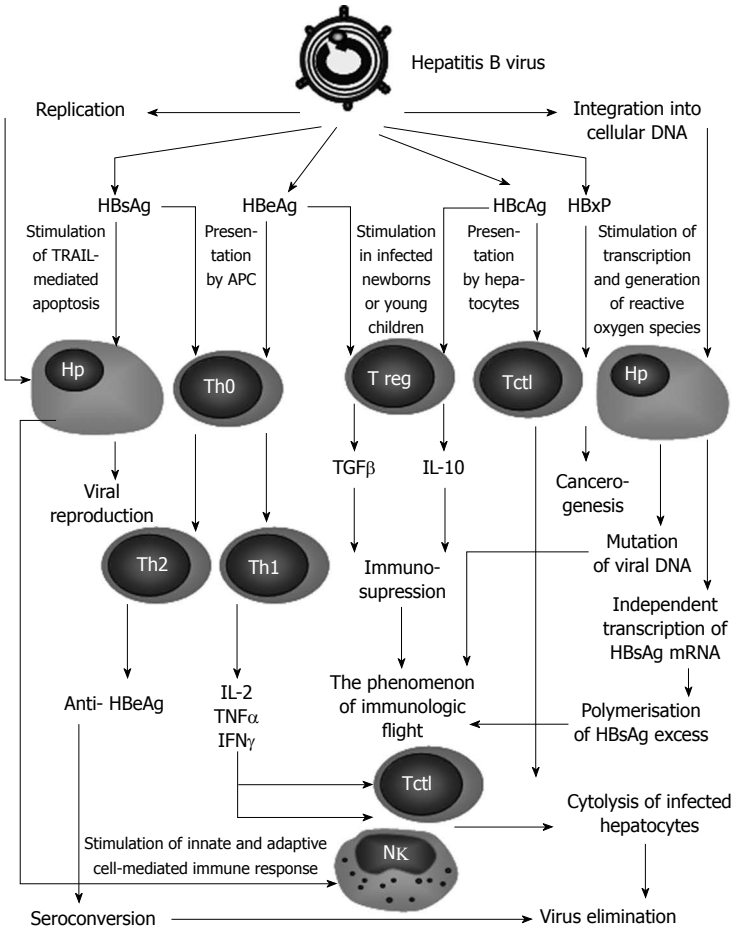

Figure 2 Structural model of hepatitis B virus protein interaction with host cells. In the course of viral replication or in integration of viral DNA into that of hepatocytes, viral proteins are synthesized in excess. These proteins presented by hepatocytes, or released when the hepatocytes undergo apoptosis, may have a regulating impact on both hepatocytes and the immune system. Hepatitis B surface antigen (HBsAg) synthesized excessively by infected hepatocytes circulates in blood and is presented by dendritic cells, inducing T-helpers mainly of the T-helper (Th)2-type[35]. Anti-HBsAg anti-bodies help to eliminate the virus, while HBsAg itself stimulates the TRAIL-mediated apoptosis of affected hepatocytes[30]. At the same time, the excessive HBsAg is produced when viral DNA integrates into the cell genome and interferes with the formation of anti-bodies (the virus immunologic flight)[25]. Hepatitis B virus core antigen (HBcAg) is presented by hepatocytes to the cytotoxic T-cells (Tctl) that induces cytolysis of the infected hepatocytes[36]. The stimulation of Tctl also may occur indirectly, with participation of Thl cytokines [interleukin (IL)-2, Interferon (IFN)-γ, tumor necrosis factor (TNF)-α] induced by hepatitis B e antigen (HBeAg)[37]. In HBV-infected newborns or young children, HBcAg, often in combination with HBeAg, effectively stimulates regulatory T cells (Tregs) *via* cytokines [transforming growth factor (TGF)-β, IL-10], suppress the immune response, facilitating virus immunologic flight[38] that is also contributed by frequent mutations of HBV when it integrates its DNA into the genome of a hepatocyte[39].

and viral load[33]. Also, association between T cell mediated damage of the hepatic tissue, and HBeAg-positivity of the patient has not been confirmed[34]. Nevertheless, every HBV protein is able to affect the immune process.

HBV PROTEINS AS INDUCERS OF IMMUNE RESPONSES AGAINST CHRONIC HEPATITIS B

In considering the induction of the immune response following HBV infection it is important to stress the influence of certain viral structural components on the immune system, which to a large extent defines the development of a chronic infection, its progress, and outcome. The main mechanisms of HBV influence on hepatocyte and lymphocyte function are provided in Figure 2.

The host immune response against antigen-presenting hepatocytes, in particular against HBcAg, mediates the pathogenesis of HBV infection. According to Roseman *et al*[40], the HBV core protein has an intrinsic ability to activate the immune system[41], in both a T cell-independent and T cell-dependent manner[42]. Many epitopes with high density and proper spacing, generated from the native core protein, can efficiently crosslink with B cell receptors[43]. Liver tissue from patients with HBV-associated acute liver failure is characterized by an overwhelming B cell response that is apparently centered in the liver-targeting HBcAg[44]. As a result, HBcAg is potentially able to induce an efficient immune response involving $CD8^+$ T cells, and direct B cell activation with the production of antiviral antibodies aimed against the infected hepatocytes. However, execution of the above-mentioned mechanism is hindered by intracellular localization of the antigen as well as its concealment in viral particles with envelope proteins[40]. Under ideal conditions, $CD8^+$ T cells are the key effector immune cells, reducing active virus replication and propagation in the course of acute HBV infection[45] by killing infected hepatocytes[29].

Li *et al*[46] demonstrated that HBcAg-specific IL21-producing $CD4^+$ T cell responses might contribute to viral control by sustaining $CD8^+$ T cell antiviral function. Therefore, one can hypothesize that small amounts of soluble HBcAg that enter the bloodstream as a result of viral particle destruction or cytolysis of infected hepatocytes may bind to B lymphocyte receptors and be presented to $CD4^+$ T cells. This ability of HBcAg to stimulate both cellular and humoral immune response has been used by some groups in designing therapeutic vaccines for chronic hepatitis B[47].

HBeAg plays a prominent role in the process of virus-host immune system interaction, particularly at the stage of viral antigen presentation and recognition by $CD4^+$ T cells[34]. This antigen serves as an important marker in immunopathogenesis of CHB. This process is divided into four stages, each of which, in addition to im-

munological shifts, is accompanied by specific clinical and morphological changes[31].

The first stage of CHB, "immune tolerance," is characterized by (1) the detection of HBeAg in patient's serum; (2) high viral load; (3) normal serum levels of aminotransferases; and (4) minimal or no inflammatory changes identified in liver biopsy[48]. The above state of immune tolerance to HBeAg is characteristic of people infected during the neonatal period or in early infancy, but also is occasionally seen in adult CHB patients[31]. Although high serum levels of HBV DNA in patients with liver disease, but with minimal or no inflammation, is believed to be a consequence of immune tolerance to HBeAg, it has been shown that HBeAg serves as an immune regulator and may foster chronic HBV infection[49]. For instance, in transgenic mice, transplacental transport of maternal HBeAg may induce a state of immunological non-responsiveness by acting as a tolerogen[50]. T cell tolerance towards HBeAg can be facilitated by central deletion of high-affinity HBe/HBcAg-specific $CD4^+$ T cells, clonal ignorance, or adaptive tolerance, resulting in ineffective cytotoxic T cell lysis of infected hepatocytes[31]. Hence, the capability of serum HBeAg to act as a T cell tolerogen and to suppress the immune response towards HBcAg may result in the reduction of HBcAg-specific liver damage during an acute infection, and in the promotion of chronic HBV infection[51]. HBeAg-specific Th2 cells preferentially evade tolerance induction as compared to their Th1 cell counterparts and therefore Th2 cells predominate above Th1 cells at this stage[49]. Regulatory T cells (Tregs) also can down-regulate effector T cells and may thus be key players in eliciting impaired immune response and development of immune tolerance[53]. HbcAg, in complex with HBeAg, acts as the basic inducer of Tregs[38]. Secretion of monomeric HBeAg in the relatively Th2-biased newborn immune system following neonatal or prenatal HBV infection (absent *in uterus* tolerance), may also have an anti-inflammatory effect on nucleoprotein-specific immune response by stimulating Th2 cytokines. The secreted HBeAg can also enter the thymus. It has been reported that HbeAg-specific Th2 cells can preferentially avoid induction of tolerance to a greater extent than HBeAg-specific Th1 cells[53].

During the second "immune clearance" stage of HBV infection, seroconversion occurs with the participation of HBeAb and a subsequent drop of HBeAg serum concentration. As a result, there is a changeover from the HBeAg-specific Th2-response to the relatively low-avidity, HBeAg-specific Th1 activation in the liver[31]. The suppression of viral replication and reduction of viral load in the blood observed after loss of HBeAg is mainly explained by a reduced cccDNA load in the liver[54]. In parallel, the secretion of interleukin (IL)-2, interferons (IFN), and tumor necrosis factors (TNF) mediates hepatocyte damage, inflammatory changes in the liver, elevated serum aminotransferase activity (to a larger extent ALT), and fibrous changes to the liver aggregate. The process passes into its active phase (CHB second stage)[31]. Several studies indicate that seroconversion is coincident with remission of the inflammatory process in the liver[55]. The end result of seroconversion is transition into immune stage 3 in the course of CHB, "inactive HBsAg carrier stage".

HBsAg carriers comprise an overwhelming group of HBV patients. Morphological changes in the liver of these patients vary, from no or minimal fibrosis, to slow cirrhosis[31,56]. Long-term epidemiologic studies have shown that after seroconversion, the majority of HBsAg carriers maintain the HBeAg negative status in combination with low or undetectable levels of HBV DNA in the blood, with a negligible activity of enzymatic hepatic systems[56]. A small group of HBsAg carriers is made up of patients with short-lived virological activity[31]. Approximately, 1%-2% of patients at this stage of the infection exhibit spontaneous HBsAg removal from the blood, independent of hepatic fibrosis[30,50]. However this event does not fully prevent decompensation of hepatic function and development of HCC[31,57].

Approximately 20%-30% of the inactive HBsAg carriers exhibit spontaneous reactivation of hepatitis B, increasing the risk of developing progressive hepatic damage and hepatic function decompensation. The reactivation of HBV is not always associated with HBeAg reversion, since HBV can lose the ability to produce HBeAg due to multiple genic mutations[31,39,58]. There are some opinions that the loss of HBeAg may represent an attempt to circumvent immune control by HBV[31,50]. The absence of circulating HBeAg results in a decrease of the specific Th2-response, and subsequent increase in the Th1-mediated liver inflammation[31,53]. Comparative studies of HBsAg seroconversion have shown that HBeAg-positive patients exhibit much higher indices of ALT and HBV DNA levels in the blood[31]. Dunn *et al*[59] theorized that liver cell damage is mediated by activated NK cells exhibiting increased levels of a TRAIL death-inducing receptor, and that this non-antigen-specific mechanism can be switched on by cytokines produced during active HBV infection. In summary, a dynamic balance between viral replication and host immune response is pivotal to pathogenesis. In this regard, Shi *et al*[31] suggested that long-term monitoring and optimal timing of antiviral therapy for chronic HBV infection can help to prevent progression of HBV-related liver disease to its later stages, particularly in patients exhibiting higher risk markers of HCC, such as serum HBV DNA load, HBeAg status, serum aminotransferase, HBV genotypes, and pre-core or core mutants.

HBxP also contributes to CHB immunopathogenesis. The protein acts as a strong transcriptional activator that can trigger malignant transformation by enhancing production of reactive oxygen species, which in turn induces higher mutation rates[60].

As mentioned above, HBV DNA has the ability to integrate and persist in the hepatocyte genetic material as minichromosomes, that can persist for a few months to several years. The process of HBV integration and repli-

cation occurs simultaneously. In this case, the integrated DNA can serve as an independent template for HBsAg mRNA synthesis, which accounts for the presence of HBsAg in infected patients in the absence of detectable HBV DNA replication[61]. During the course of hepatocyte division, HBV DNA is asymmetrically distributed between the daughter cells. This makes it possible for the virus to create mutated copies of the genome and provide for long-term intrahepatic survival of the mutant virus even under the conditions of antiviral therapy[34]. Thus, the integration process does not support virus particle reproduction, but instead contributes to long-term HBV persistence in hepatocytes.

There is an additional molecular mechanism for the virus to "avoid" the immune system. HBsAg produced in hepatocytes can efficiently polymerize, thereby becoming resistant to degradation by proteasomes in the endoplasmic reticulum. This effectively blocks presentation of the protein to CTL by the class I major histocompatibility complex, and allows the virus to remain "invisible" to the immune cells[62]. Hence, nuts and bolts for HBV infection chronicity lie in the molecular biology of the virus, its ability to mutate and interaction of HBV with the immune system of the host accompanied by immune avoidance[63,64].

INNATE IMMUNE RESPONSE AGAINST CHRONIC HEPATITIS B

HBV can suppress the production of primary cytokines (IFNα/β and IFNγ) by cells involved in the innate immune response, or by specifically modulating the cellular response to IFN[65], and activation of other mechanisms[66,67]. Subsequently, an adaptive T cell response is triggered[68,69].

Immune cells producing IFNα/β and IFNγ play an important role in mounting an innate immune response against HBV under the conditions of a chronic infectious process[21]. Macrophages, natural killer cells (NK cells), NKT, TCRγδ$^+$ T cells secreting IFNγ, and the production of IFNα/β by plasmacytoid dendritic cells (pDCs)[35,70,71] and infected hepatocytes all function to enhance a systemic antiviral response[29,72]. On the other hand, there exists an experimentally confirmed CD8$^+$ specific T cell-induced inflammation of hepatic tissue that is actively supported and aggravated by the above-mentioned non-specific cellular components of the immune system present in hepatic cellular infiltrate[32,73]. Such a dual approach requires a detailed functional analysis of the innate immune response against chronic hepatitis B.

The macrophage-mediated antiviral immune response in CHB is mainly provided by Kupffer cells and circulating monocytes.

Kupffer cells perform a number of roles in their capacity as the resident macrophages of the liver. These roles include phagocytosis, antigen recognition and presentation, and secretion of proinflammatory mediators[32]. The exact role of Kupffer cells in HBV infection is only partially understood. In the HBV transgenic mouse model, Kupffer cells produce the chemokines CXCL9 and CXCL10, which assist in the recruitment of inflammatory cells to the liver[74]. IL-12 and IL-18 made by Kupffer cells can stimulate NK cells to produce IFNγ[75,76].

HBeAg-positive chronic hepatitis is also associated with the disruption of monocyte functions, including a significant decrease in expression of the key component of innate antiviral immunity - Toll-like receptors type three (TLR3)[77-79], which brings about HBV persistence by blocking non-specific defense processes[79]. There is no debate about the ability of HBcAg and HBeAg in CHB to stimulate IL-10 production by peripheral blood mononuclear cells. This cytokine aggravates immune tolerance to HBV[63] and the development of anti fibroid effects in the liver[80]. The pool of IL-10 secreting cells in this viral disorder is formed by 26%-35% by T cells (mainly, CD4$^+$and CD8$^+$), 62%-70% by monocytes and less than 1% by B cells, whereas in healthy subjects exclusively blood monocytes have the ability to produce IL-10 when stimulated by HBcAg[63].

These data that indicate IL-10 immunosuppressive effects have been indirectly confirmed in the course of clinical observations, and suggest in particular the worsening of CHB prognosis in case of a significant decrease in the T cell/monocyte ratio in the blood[81].

Dendritic cells (DCs) are specialized antigen-presenting cells that choreograph immune responses. In viral hepatitis, dysfunction of DCs from peripheral blood has been reported[82]. Maturation of DCs from peripheral blood of CHB patients after incubation with cytokines is lower than that of normal subjects. CHB patients have lower expression of HLA-DR and co-stimulatory molecules[49], leading to low allostimulatory function of DCs. The peripheral(p) DC population is known to be heterogeneous, both in generation mode and origin, that makes certain DC categories especially interesting in terms of immune response induction in chronic hepatitis B.

Recently, HBV itself was shown to inhibit the functions of pDCs[83]. The reduced number and impaired function of circulating pDCs in patients with CHB may be linked to disease progression. The isolated pDCs from CHB patients produced lower levels of IFNα and expressed lower levels of CD80 and CD40 compared to those of the healthy controls[84]. Moreover, the pDCs frequency level was inversely correlated with serum ALT levels in the HBV infected patients[84]. Type 2 precursor pDCs, which are the most important cells in antiviral innate immunity, are also reported to exhibit quantitative and qualitative impairment in patients with chronic HBV infection[35]. Importantly, in acute-on-chronic hepatitis B liver failure patients, activated pDCs accumulate in large numbers in the liver, and regulate local immune response against chronic HBV infection[85].

Both HBV particles and purified HBsAg may possess immunomodulatory capability and directly contribute to myeloid DCs (mDC) dysfunction[86]. HBV- induced deficiency of monocyte-derived dendritic cells (MoDC)

leads to impaired Th1 cell responses *in vitro*[87]. It was also shown that MoDC impairment correlates with severe liver damage in acute HBV infection. Here, TLR3/IFNβ expression in MoDCs may be a potential diagnostic marker[78]. It is interesting to note that impaired function of MoDCs from patients with CHB could be reversed by inhibiting viral replication with nucleoside analogs such as lamivudine[87]. These data indicate that DCs in patients with CHB exhibit impaired function that leads to inadequate T cell response to HBV, which could be a potential mechanism for chronic HBV infection.

Most studies of DCs as part of CHB immunopathogenesis were carried out when the disease was progressing. Ratnam *et al*[32] stated that "the DCs in other stages of chronic hepatitis B are not only capable of generating and coordinating adaptive immune responses but also play a role in inducing tolerance to both self and foreign antigens". In this context it is important to emphasize the capability of DCs to induce Tregs in CHB patients. Initial studies in TCR transgenic mice have shown that mature DCs are specialized antigen-presenting cells for expanding antigen-specific $CD25^+$ $CD4^+$ Tregs[67]. The DC-expanded Tregs continue to express high levels of forkhead box P3 (Foxp3) protein. When triggered by a specific antigen, these Tregs act on immature DCs *via* a feedback mechanism to block the upregulation of CD80 and CD86 co-stimulatory molecules[67]. However, these findings are highly controversial. Experimental studies of intrahepatic DCs from HBV-transgenic mice reveal impaired T-cell proliferative capacity and production of IL-12, IL-6, IFNγ, and TNFα[43].

Thus, DCs play a major role in CHB immunopathogenesis and modulate their function depending on the stage of the infection process. Especially important in this context is the interaction between DCs and other cells of the innate or adaptive immune response. A key role in the regulation of DC function in CHB patients is played by the intrahepatic pool of natural killer cells (NK cells, Pit cells) that make up 30%-40% of all lymphocytes in the inflammatory infiltrate[59,88]. The number of intrahepatic NK cells in CHB patients is 10-12 fold higher, compared to healthy controls[73].

Activated NK cells function *via* two key mechanisms: direct cytotoxicity towards infected cells through cell-cell contact (CD56-bright subset) and production of inflammatory cytokines (CD56-dim subset)[88,89]. The mechanism of NK antiviral cytotoxicity appears to be organ-dependent. Receptor-mediated cell death *via* ligand-receptor pairs belonging to the TNF superfamily is mediated by TNF-related apoptosis-inducing ligand (TRAIL), expressed on infiltrating lymphocytes. Interaction with TRAIL death-inducing receptors (TRAIL-R1 and TRAIL-R2) on hepatocytes likely plays an important role in liver damage[59]. Cytokines produced by NK cells include those with direct antiviral activity, such as IFNγ and TNFα, and those with immunomodulatory activity[90], such as IL-3, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor[32]. The induction of infected cell death in the liver appears to be not only due to NK cells but also by a synergistic effect of two or more cytokines. IL-8 enhances the expression of the apoptosis receptor on hepatocytes, while IFNα in turn enhances expression of the ligand for the same receptor on NK cells[59,91]. These cytokines have been confirmed to be involved in the antigen-nonspecific liver damage, as well as in the regulation of NK cell migration into the liver when the inflammatory response increases[59].

Studies using the transgenic mouse model found that the HBsAg mice were much more sensitive to liver injury in response to both polyI:C and concanavalin A treatment. Notably, this oversensitivity to liver injury was dependent on the accumulation of intrahepatic NK cells, and the IFNγ produced by them[92]. The effect of concanavalin A appeared to be mediated by the stress-induced expression of NKG2D, an activating killer cell receptor on hepatocytes, which is independent of Kupffer cell and IL-12 activity[93].

It has been clinically established that excessive NK-cytotoxic characteristic of CD56-dim NK cells is associated with an unfavorable prognosis of viral hepatitis[94], while at lower viral loads the secretory CD56-bright subpopulation in the liver remains dominant[95]. NK cells can be activated in the liver *via* Toll-like receptors that have viral nucleic acids as ligands[96]. More often, the effector functions of NK cells are integrated by balancing signals from activating and inhibiting natural killer receptors on the surfaces of NK cells that interact with class I MHC molecules[97]. Therefore, certain cytokines may enhance the antiviral activity of NK cells. For example, IFNα is a promoter of cytotoxic reactions with the participation of these cells, while IL-8 induces IFNγ production, and IL-2 helps activate NK cells[59,91].

NK cell participation in CHB immune pathogenesis occurs *via* active contact and paracrine interaction with other cells. Studies have shown that NK interaction with hepatocytes occurs *via* the activating lectin receptors NKG2D during HBV-related damage of the liver[54,93,98]. Expression of NKG2D ligands (Rae-1 and Mult-1) in hepatocytes is markedly enhanced, and strongly activates hepatic NK cells *via* NKG2D/Rae-1 or Mult-1 recognition[93].

However, intercellular interactions with NK cells do not always lead to direct cytolysis of virus-infected cells. For instance, NK interactions with HLA-E expressing hepatocytes *via* the NKG2A-inhibiting receptor leads to dendritic cell-mediated induction of $CD4^+$ $CD25^+$ T cell activity and appearance of their regulatory behaviors[99]. This happens through the NK cell immunosuppressive cytokines IL-10 and TGFβ, but not through the direct NK cell contact with DCs. Decreased secretion of TNFα as a TGFβ antagonist also was observed[100]. The regulatory T-cells induced by NK-primed DCs are capable of inducing a suppressor effect *via* the negative co-stimulation of Programmed Death-1 (PD-1) isolated from $CD4^+CD25^+$ T cells. The PD-1-mediated signals

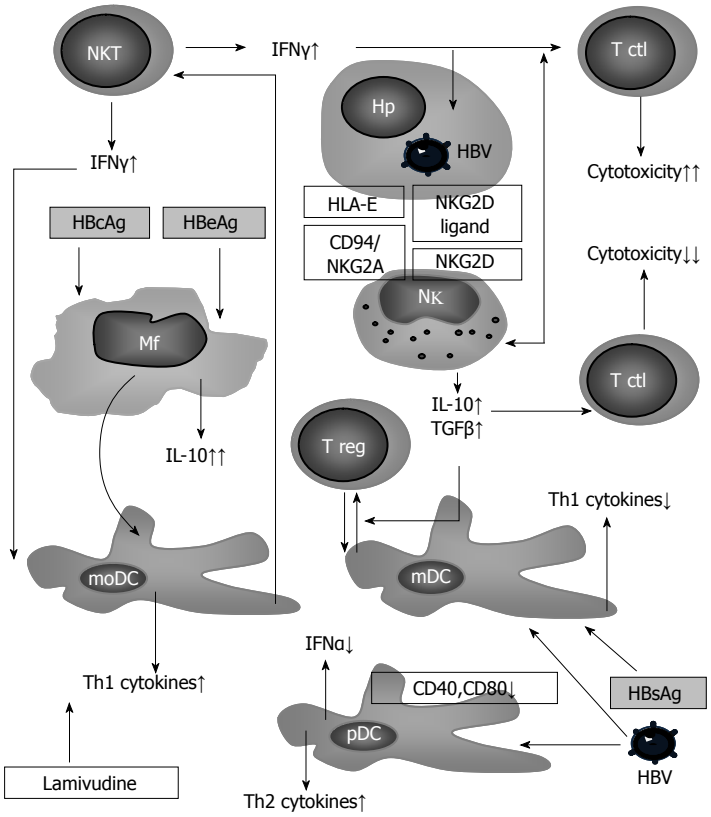

Figure 3 Intracellular interactions in the innate immune system in chronic hepatitis B patients. An infected hepatocyte (Hp) expresses ligands for inhibiting (CD94/NKG2A) and activating (NKG2D) receptors of natural killer (NK) cells, which stimulate these cells to secrete immunosuppressive cytokines (IL-10 and TGFβ), assisting in the induction of regulatory T cells (Tregs) with the participation of mDC[98]. Under the influence of viral antigens, pDC decreases its adhesive properties as well as its abilities to produce interferon (IFN)-α[35,107,108], thus creating ideal conditions for the involvement of Th2 in the immune response. Simultaneously, there is monocyte stimulation to produce immunosuppressive IL-10. Viral antigens also contribute to the differentiation of monocytes to the dendritic cells[41]. Monocytic dendritic cells (moDC) induce Th1 defects that are characteristic of chronic hepatitis C patients[109], and that may be corrected by treatment with lamivudine[87]. NKTs, actively producing IFNγ in chronic hepatitis B (CHB)[102], assist in the increase of efficacy of cell-mediated immune response with participation of Th1 and cytotoxic T cells (CTL)[110].

induce anergy of $CD8^+$ T cells and the attenuation of the antiviral response mediated by CTL during chronic viral infection[99,101].

NKT cells are a T lymphocyte subset expressing classic NK cell markers. They comprise approximately one-third of the intrahepatic T cells. They also can be induced to produce IFNγ in response to NK cell stimulation and IL-12. Interestingly, NKT cells produce IL-4 during innate immune responses[102].

NKT cells can exhibit three phenotypes that differ in the functions of cytokines they produce: (1) $CD4^+$; (2) $CD8^+$; and (3) CD4/CD8 or double-negative (DN) NKT[103]. The $CD3^+CD56^+CD4^+$ cells perform immunoregulatory functions by actively producing either IFNγ (Th1 immune response induction) or IL-4 (Th2 response regulation). The second subpopulation of NKT ($CD3^+CD56^+CD8^+$) that produces IL-10 and TGFβ is capable of immunosuppression. The double-negative NKT ($CD3^+CD56^+$CD4-CD8-) has antigen-identifying (*via* CD1d-restricted mechanism) and cytotoxic (NK) functions with an appropriate set of perforins and granzymes[104]. Evidence indicates a prevalent $CD8^+$ subpopulation among NKT cells in chronic hepatitis B[105].

DCs prove to be the most effective inducers of IFNs and NKT cell secretions in the liver in CHB[102]. The antiviral activity of NKT cells in HBV infection in turn is associated with a rise in intrahepatic production of IFNγ and IFNα/β. IFNγ has also been shown to up-regulate MHC class 1 expression on hepatocytes, and mediate macrophage- and DC-dependent inhibition of viral replication[89]. NKT cells rapidly activate NK cells in the liver that have a synergistic cytokine-producing effect on IFNγ. All these processes of intrahepatic NKT activation and their antiviral effects proceed quickly because of their massive presence in the liver[106].

According to the present analysis, the quantitative composition and functions of innate immune cells have pronounced effects on the causative agent in chronic hepatitis B. Figure 3 describes the processes and intracellular interactions involved in the development of CHB.

ADAPTIVE IMMUNE RESPONSE IN CHRONIC HEPATITIS B PATIENTS

The development of the adaptive immune response is primarily due to heterogeneity of the T and B lymphocyte systems. The literature indicates that CHB is associated primarily with disturbances in proliferation processes, cytokine production, and the effector cytotoxic function of HBV-specific T cells in combination with certain shifts in humoral immunity[29,32]. At the same time, most authors view the $CD4^+CD25^+$ Tregs as probable candidates for suppressing the antiviral response to the infection[37,52].

Known are several subsets of regulatory $CD4^+$ Tregs that express the receptor CD-25, secrete IL-10 and/or TGFβ, IL-35 leading to immunosuppression. The marker of most Tregs is the FoxP3 molecule-also known as scurfin-which is involved in immune response. A member of the Fox protein family, FoxP3 appears to function as a master regulator (transcription factor) of development and function of Tregs[111]. While the precise control mechanism has not yet been established, Fox proteins

belong to the forkhead/winged-helix family of transcriptional regulators and are believed to exercise control *via* similar DNA-binding interactions during transcription. In the Tregs model, the FoxP3 transcription factor occupies the promoters for genes involved in regulatory T-cell function, and may suppress transcription of key genes following stimulation of T cell receptors[112].

In human, Tregs make up 5%-10% of the $CD4^+$ cells and are characterized by a low level of proliferation in response to a specific stimulation by the T-cell receptor (TCR). $CD4^+$ $CD25^+$ Tregs produce IL-10 but not IFNγ under anti-CD3 stimulation, and are capable of suppressing Th1 and Th2 responses[37]. In HBV infection, the inhibiting effect of Tregs on immune cells makes it possible for the virus to persist[37,113]. Simultaneously, the levels of TGFβ increase leading to fibrous changes in the liver[114]. It should also be noted that $FoxP3^+$Tregs (1) show diverse phenotypes; (2) occur in both $CD4^+$ and $CD8^+$ T cell subsets; and (3) express CD25 (IL-2 receptor chain) and/or cytotoxic T-lymphocyte antigen 4 (CTLA-4) in addition to Foxp3[115]. In HBV infection, HBeAg-positive patients with high HBV DNA levels in the serum show elevated numbers of $CD4^+CD25^+$ Treg cells in the blood compared to patients with acute or chronic hepatitis C virus (HCV) infection[116]. Significant accumulation of $CD4^+CD25^+FoxP3^+$ Tregs in the liver is seen in patients with chronic HBV infection. Furthermore, patients with a high viral load have a higher percentage of Treg cells in the liver[117], suggesting a role for intrahepatic Tregs in suppressing antiviral immune responses in the liver in chronic HBV infection. Additionally, the expansion of $CD4^+CD25^+$ Tregs and the enhancement of the suppressor function of $CD4^+CD25^+$ Tregs induced by HBV infection-related factors could suppress the anti-tumor immune response and inhibit tumor immune-surveillance, which may be involved in the immunopathogenesis, from CHB to hepatocellular carcinoma[45,118].

As indicated above, the main inducer of Tregs in chronic hepatitis B is HBcAg[38] as it initiates interactions among innate immune cells, specifically DCs, NKs and NKTs. Apparently, the developments discussed previously are likely to be characteristic of a chronic process at the stage of immunological tolerance, which results in progression of the disease. At the stage of immunological clearance in HBeAg-positive hepatitis, a completely formed $CD4^+CD25^+FoxP3^+$ Tregs pool operates mainly in the liver through its impact on blood cells. However, as the infection expands, the T lymphocyte phenotypic profile undergoes substantial changes.

Some evidence exists that with a rise of viral load and HBeAg in the serum of CHB patients, there is a significant decrease in $CD3^+$ and $CD4^+$ cells, and the $CD4^+$/$CD8^+$ ratio, but with an increased number of $CD8^+$ cells compared to uninfected controls[34]. Meanwhile, as shown in Figure 3, a major component responsible for the immunological shifts observed in CHB appears to be excessive production of certain anti-inflammatory cytokines, specifically IL-10, which positively correlates with the activity of hepatic ALT and detectable viral DNA in blood[63].

There are additional mechanisms of inhibiting T lymphocyte function, which involve secretion of immunosuppressing cytokines and intercellular contacts. According to Shimizu *et al*[119], PD-1 is a surface receptor critical for the regulation of T cell function[120]. Binding to PD-1 by its ligands, PD-L1 and PD-L2, results in the antigen-specific inhibition of T cell proliferation, cytokine production and cytolytic function, leading to exhaustion of T cells. In the liver, PD-1 is expressed on lymphocytes, whereas PD-L1 is expressed on lymphocytes, hepatocytes and sinusoidal endothelial cells, while PD-L2 is expressed on Kupffer cells and DCs[121]. HBeAg-positive patients with elevated HBV DNA levels in the serum exhibit increased PD-1 and CTLA-4 expression on HBV-specific $CD8^+$ T cells[122]. Moreover, PD-1 expression on $CD4^+$ T cells correlates positively with serum HBV DNA load in CHB patients[123]. Intrahepatic HBV-specific $CD8^+$ T cells express higher levels of PD-1, and upregulation of intrahepatic PD-1/PD-L1 is associated with liver inflammation and ALT elevation. Inhibition of PD-1/PD-L1 has been suggested as a potential therapeutic approach for the control of hepatitis B[119].

Present literature indicates that marked deviations found in the composition of helper $CD4^+$ T cells and $CD8^+$ CTLs in CHB[34,124] not only are quantitative but also functional in nature[97], which calls for their separate assessment in terms of the disease stage, their location (in peripheral blood or the liver) and capacity to show high specificity or alloreactivity.

In peripheral blood, HBV-specific helper T lymphocytes and CTLs are barely detectable in patients with chronic hepatitis B[4]. This is probably due to exhaustion, because of high viral load or tolerance to HBV[119]. In contrast, several studies have characterized intrahepatic $CD4^+$ and $CD8^+$ T lymphocytes in CHB. Intrahepatic $CD4^+$ T lymphocytes in patients with CHB have been found to contain Th0 cells, which produce IFNγ, IL-4, and IL-5, and differs from cells in the livers of patients with chronic hepatitis C, which are mostly Th1 cells[125]. $CD4^+$ T lymphocytes that produce IL-17 infiltrate into the livers of patients with CHB and are involved in liver inflammation[126].

It was also demonstrated that a high content of IL-17-producing $CD4^+$ T cells was observed not only in the liver but also in the blood of CHB patients, and is correlated with a high level of IL-27 in serum[127]. It is possible that these cells can help to sustain the inflammatory changes in the liver and perform certain protective functions. Zhang *et al*[128] showed that the increase in Th17 cells and concomitant decrease in Tregs creates an imbalance that negatively correlates with disease progression. Kitani and Xu[129] put forward an idea that Tregs themselves may be the source of Thl7 differentiation. Moreover, the resulting imbalance is conducive for the elimination of Tregs involved in immune pathogenesis of hepatocellular carcinoma.

Table 1 Immunologic characteristics of the stages of chronic hepatitis B

Stage of CHB	Markers of stage	T cell subsets				
		Th1	Th2	Th17	Treg	CTL
Immune tolerance stage	HBsAg+ HBeAg+ HBeAb- HBV DNA + ALT normal Liver histology: normal or mild inflammation[56]	Inactive HBe/HBc-specific Th1[53]	Predominance of HBeAg-specific Th2 cells. Predominance of anti-inflammatory cytokines - IL-4, IL-5, IL-10[53,56]		Significant accumulation of CD4+CD25+ FoxP3+ Treg cells in the liver. CD8+ CTLA-4+ FoxP3+ Treg cells present[117]	
Immune clearance stage	HBsAg+ HBeAg+ HBeAb- HBV DNA + ALT ↑ Liver histology: active inflammation[56]	Intrahepatic CD4+ T cells are mostly Th1 cells. Predominance of IL-2, IFNγ, TNFα cytokines[141]	Inactive HBe-specific Th2 clones with low avidity[141]	High content of Th17 in the liver[126] and in the blood[127]	Treg cells elevate in the beginning and then fall in the liver and elevate in the blood[123,128,132]	HBcAg-specific CD8+ CTLs increase in the liver[34] but not in the blood[56,142]
Inactive HBsAg carrier stage	HBsAg+ HBeAg- HBeAb+ HBV DNA+ ALT normal/↑ Liver histology: mild inflammation or inactive cirrhosis[56]	Predominance of inflammatory Th1 cells[56]				HBV-specific central memory CD8+ T cell response[143]
		Low HBV-specific immune responses[84]				
Reactivation stage	HBsAg+ HBeAg- HBeAb+ HBV DNA +/- ALT normal/↑ Liver histology: from normal to cirrhosis and hepatocellular carcinoma[56]	Predominance of inflammatory Th1 cells[56]	HBeAg-specific Th2 cells fall down[56]			CD8+ CTLs fall down[144]
		Anergy of HBc/HBeAg and HBeAg specific T-cells in the liver[117]				
		Serum cytokine levels (interferon IFNγ, TNFα, IL-1β, IL-4, IL-12, IL-10, IL-2, IL-5, IL-8) are evaluated[145]				

CHB: Chronic hepatitis B; Th: T helper; Tregs: Regulatory T cells; CTL: Cytotoxic T cells; IL: Interleukin; ALT: Alanine transaminase; INF: Interferon; TNF: Tumor necrosis factor; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBcAb: Hepatitis B virus core antibody; HBV: Hepatitis B virus.

It was shown that, along with viral antigens, anti-inflammatory cytokines (such as IFNγ) increase the expression of one of the apoptosis membrane factors (TRAIL) on the surface of $CD4^+$ and $CD8^+$ T lymphocytes[92]. A reference can be made to the evidence obtained by Wang *et al*[130], who investigated the potential role and mechanism of microRNA miR-146a in regulating T cell immune responses in CHB. They found that miR-146a expression in T cells is significantly up-regulated in CHB compared to healthy controls, and that miR-146a levels correlate with serum ALT levels. STAT1 (signal transducers and activators of transcription 1) was identified as a miR-146a target that is involved in antiviral cytokine production and the cytotoxicity of $CD4^+$ and $CD8^+$ T cells. The *in vitro* blockage of miR-146a in T cells in CHB greatly enhanced virus-specific T cell activity. Similarly, in CHB and HBV-associated acute-on-chronic liver failure patients, miR-233 is significantly increased, whereas in HBeAg positive patients, liver-specific miR122 and miR149 are both significantly up-regulated[131].

The immunopathogenesis of CHB is crucial for a number of other events. On one hand, some evidence for an association between a high viral load in CHB, and the production of IFNγ, TNFα and cytokines, including IL-18, by macrophages, dendritic cells and $CD8^+$ cells[3,132]. On the other hand, the presence of the HBxP significantly induces the impact of TNFα on hepatocyte damage *via* initiation of apoptosis[132,133]. An etiological role of enhanced expression of IFNγ has been proposed in the development of induced hepatitis and its ability to increase TNFα mediated hepatocyte damage[3,134]. Moreover, the given cytokines, by stimulating the release of chemokines by hepatocytes, contribute to the enhancement of non-specific infiltration into the liver by T-lymphocytes, B-lymphocytes, NK cells, NKT cells, neutrophils, monocytes, macrophages, and dendrites[3,73,135]. To prevent the severe impairment of the liver in the presence of excessive IFNγ, the system triggers a protective suppression mechanism through stimulating the production of IL-10 by the peripheral blood monocytes. This contributes to the cellular immune response insufficiency, and the uncontrolled replication of the virus in CHB[63,136]. Thus, the mechanisms of immune protection and immune damage of hepatocytes develop simultaneously.

It is believed that factors for functional failures on the part of $CD8^+$ cells in CHB patients may include not only the high level of anti-inflammatory cytokines, but also the exhaustion of nutritive components (*e.g.*, the perturbation of L-arginine metabolism)[137,138] necessary

for proper functioning of T-cells[139,140]. Accumulation of toxic metabolites (*e.g.*, tryptophane catabolites) in the liver also interferes with the $CD4^+$ cell function[3]. The data pertaining to the prevalence of subsets of T lymphocytes at different stages of CHB development according to their effector functions and clonal specificity are summarized in Table 1.

Intriguingly, since the levels of some immune markers change significantly during clinical course of the disease and treatment, these have been reported as indices to guide clinicians in predicting prognosis and treatment decisions. After receiving entecavir therapy, the restored cytokine-producing capacity of NK cells participates in viral clearance in CHB patients, which could be monitored by CD56-dim NK cell activation[146]. During *in vitro* IFNα treatment, the dampened Z39Ig (a novel inhibitor of the B7 superfamily) signals from macrophages are also found to contribute to CHB clinical therapy[147]. Restoration of peripheral mDCs during adefovir treatment and plasmocytoid dendritic cells during IFNα therapy may represent prognostic markers for favorable responses[148,149]. A recent study further reported that during lamivudine therapy, patients may only exhibit a transient restoration of circulating DC[131].

CONCLUSION

The combined outcome of all the processes described above envisions the immune system as being unable to ensure the appropriate level of specific response, which leads to very high number of circulating viruses that are virtually impossible to be eliminated by the humoral response alone[34]. The programmed death of immune cells, primarily $CD8^+$ lymphocytes[140], is induced by exhausted production of IL-2 in the liver[3,150]. This causes worsening of the functional defects of lymphocytes, further reducing the efficacy of specific immune reactions[144,101].

Thus, at the heart of CHB development lies a gamut of pathogenic mechanisms responsible for the disturbed immune response. A wave-like modulation in cytotoxic and secretory functions, the exhaustion of innate and adaptive immune responses, and a changed induction in Treg suppressor and Th17 inflammatory functions are a few known immunologic mechanisms in the CHB pathogenesis. An in-depth understanding of immunopathogenic mechanisms induced by distinct antigen components of HBV that cause both chronic hepatitis B and its unfavorable outcomes will provide the basis for driving explicit and prognostically meaningful methods of immunodiagnostics as well as effective treatment and prevention of the disease.

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