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**Restoring homeostasis of CD4+ T cells in hepatitis-B-virus-related liver fibrosis**

Cheng LS *et al.* Homeostasis of CD4+ T cells

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**Abstract**

Immune-mediated liver injury is widely seen during hepatitis B virus (HBV) infection. Unsuccessful immune clearance of HBV results in chronic hepatitis and increases the risk of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). HBV-related liver fibrosis (HBVLF), occurring as a result of HBV-induced chronic hepatitis, is a reversible, intermediate stage of chronic hepatitis B (CHB) and LC. Therefore, establishing the pathogenesis of HBVLF is of practical significance for achieving better clinical outcomes. Recently, the homeostasis of CD4+ T cells was considered to be pivotal in the process of HBVLF. To better uncover the underlying mechanisms, in this review, we systematically retrospect the impacts of different CD4+ T-cell subsets on CHB and HBVLF. We put emphasis on CD4+ T-cell homeostasis, of which the balance between regulatory T (Treg) and T helper (Th) 17 cells is the most important. In addition, we discuss some cytokines associated with Treg and Th17 cells such as interleukin (IL)-17, IL-22, IL-21, IL-23, IL-10, IL-35 and IL-33, as well as some surface molecules such as programmed cell-death protein (PD)-1, cytotoxic T lymphocyte-associated antigen (CTLA)-4, T-cell immunoglobulin domain and mucin domain-containing molecule (TIM)-3 and cannabinoid receptor (CB) 2 that have potential therapeutic implications affecting the homeostasis of CD4+ T cells in CHB and HBVLF.

**Key words**: Homeostasis; Regulatory T cells; T helper 17 cells; CD4+ T cells; Liver fibrosis; Chronic hepatitis B; Pathogenesis; Therapy

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**Core tip:** Hepatitis B virus(HBV)-related liver fibrosis (HBVLF) is a reversible, intermediate stage of chronic hepatitis B and liver cirrhosis. The homeostasis of CD4+ T cells, especially the balance between regulatory T (Treg) and T helper (Th) 17 cells is pivotal in the process. Therefore, uncover the underlying mechanism of CD4+ T cell-homeostasis regulating HBVLF is of importance to achieve better clinical outcomes. Besides, we discuss some Treg and Th17 cell-related cytokines as well as some surface molecules that have potential therapeutic implications affecting the homeostasis in chronic HBV infection.

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**INTRODUCTION**

Nowadays, > 350 million people worldwide are chronically infected with hepatitis B virus (HBV). According to the World Health Organization, HBV puts people at high risk of death from liver cirrhosis (LC) and hepatocellular carcinoma (HCC), thus causing a heavy global health burden. Commonly, HBV is hepatotropic but not-cytopathic, and interaction between HBV, hepatocytes and host immune responses determine the natural history of infected individuals[1]. CD4+ T cells play key roles in HBV infection. On the one hand, they have a substantial impact on the clearance of HBV by aiding cytotoxic CD8+ T cells, B cells and natural killer (NK) T cell functions[2]. On the other hand, they also contribute to the pathogenesis of inflammation progression via production of an array of proinflammatory and pro-fibrotic cytokines[2,3].

Liver fibrosis is recognized as a wound-healing response driven primarily by the development of inflammation in response to various parenchymal injuries[4]. Hepatitis B virus-related liver fibrosis (HBVLF) is a reversible, intermediated stage of chronic hepatitis B (CHB) and LC[5]. As conventional subsets of CD4+ T cells, the roles of T helper (Th)1 and Th2 cells have been long known. Th1 cells are often defined by their high production of interferon (IFN-γ), which helps to develop an efficient, specific antiviral immune response and attenuate tissue fibrosis[6,7]. Th2 cells secret abundant interleukin (IL)-4, IL-5 and IL-13, which suppress the Th1-type immune response, thus resulting in persistent HBV replication and chronic liver immunopathology, and directly involved in fibrogenesis[6-8]. However, detailed study of the immune microenvironment in liver fibrosis has shown that the Th1/Th2 dichotomy is no longer appropriate. Nowadays, along with identification of new subsets and phenotypic characteristics, the crucial roles of CD4+ T-cell subsets and their homeostasis are widely recognized and extensively researched in the progression of HBV-related chronic hepatitis and liver fibrosis.

**CD4+ T-CELL SUBSETS AND THEIR IMPACT ON HBV-RELATED CHRONIC HEPATITIS AND LIVER FIBROSIS**

On the basis of characteristic transcription factors and unique cytokine profiles, as well as functional properties, CD4+ T cells can be further subdivided into a few new subsets, including Th17, Th9, Th22, T follicular helper (Tfh) cells and regulatory T (Treg) cells, in addition to Th1 and Th2 cells.

***Th17 cells***

IL-17 and its potential role in immunity was discovered two decades ago[9]; Th17 cells were defined as an independent lineage of helper cells in 2005[10,11]. Since then, IL-17 and Th17 cells were extensively studied aimed at understanding their properties and roles. At present, the pathogenic role of Th17 cells in promoting liver injury and fibrosis is widely recognized[12-15]. During chronic HBV infection, peripheral and intrahepatic Th17 cells are increased in patients with CHB or HBV-related acute-on-chronic liver failure (ACLF), and IL-17 expression is positively related to the severity of liver injury and inflammation progression[12,13]. Besides, Th17 cells are also found to increase with the severity of liver fibrosis in humans and mice[14,15].

Till now, the pathogenesis of Th17 cells aggravating liver fibrosis has not yet been fully elucidated. Several studies have pointed out that IL-17 has an effect on hepatic stellate cells (HSCs), through recruiting neutrophils and monocytes[14-17]. However, the whole is greater than the sum of its parts. Th17 cells with retinoid orphan nuclear receptor γt (RORγt) as the specific transcriptional factor, are differentiated from naïve CD4+ T cells in the condition of transforming growth factor (TGF)-β plus IL-6[10,11]. Besides, IL-21 may allow amplification of Th17 cells with or without IL-6 and TGF-β, and IL-23 is indispensable for the proliferation and final function of Th17 cells[18-22]. After activation, Th17 cells secrete a mixture of cytokines such as IL-17, IL-21, IL-22, IL-6, IL-9 and tumor necrosis factor-α (TNF-α). Although most Th17-mediated pathogenic effects are attributed to the increased production of IL-17, the impact of Th17 cells is more complex than IL-17-mediated effects.

IL-22 is mainly produced by Th17 cells, and exerts hepatoprotective or pathological effects under different settings of liver diseases, such as acute liver damage induced by carbon tetrachloride (CCl4), concanavalin A (ConA) or Fas ligand, alcoholic liver diseases, and chronic hepatitis caused by HBV or hepatitis C virus (HCV) infection[23-26]. In HBV-LC patients, Zhao *et al*[26] found that IL-22 was positively related to hepatitis and fibrosis, and using an HBV transgenic mouse model, they suggested that upregulated IL-22 exacerbated chronic hepatitis and fibrosis via promoting Th17 cell recruitment[26]. Other researchers have pointed out that the predominance of the pathological over the protective function of IL-22 in patients with HBV was due to its function in regulating upstream of chemokine expression to recruit inflammatory cells into the liver[23]. However, there are also some researchers have observed that IL-22 along with chemokines such as CXCL9 and CXCL10 were significant reduced in more severe liver injury during CHB infection[27].

Another example is IL-21. Recent studies have indicated that both increased circulating IL-21+CD3+CD8- T cells and intrahepatic IL-21 are correlated with the severity of liver damage in patients with active CHB, HBV-related LC and HBV-related ACLF[28-30]. Besides, administration of IL-21 *in vitro* has seen more activation of HSCs, thus facilitating the fibrogenesis of LC[29].

The effects of Th17 cells on HBV-related liver injury and fibrosis are comprehensive, and need to be further elucidated. Moreover, there are still mysteries surrounding Th17 cells. Apart from the integrated effects of different Th17-related cytokines, other source of these cytokines such as non-Th17-derived IL-17, produced by neutrophils, NKT cells, macrophages, or γδT cells may add difficulties in identifying the exact roles of Th17 cells in liver fibrosis[31]. Besides, in recent years, the plasticity of Th17 cells has been widely reported during inflammation[32,33], which increases the importance of cellular crosstalk between different CD4+T subsets.

***Treg cells***

CD4+CD25+ Treg cells are one of the specific lineages of CD4+T cells characterized by TGF-β and IL-2-induced Forkhead box P3 (Fox)P3[34]. Treg cells exhibit immunosuppressive and self-tolerant functions by direct cell contact or via secreting inhibitory cytokines such as IL-10, TGF-β or IL-35.

IL-10 can inhibit Th1 and Th2 responses through antigen presenting cells (APCs)[35]. It also prevents the induction of a Th17 response, but is limited in suppressing an already established Th17-predominant chronic inflammation[36]. During HBV-related disease progression, IL-10 may be one negative feedback mechanism to regulate proinflammatory Th17 responses[37]. Moreover, activated HSCs produces more IL-10, which constrains its collagen production, thus blocking the progression of liver fibrosis[38].

IL-35 is a novel inhibitory cytokine of Treg cells, and has been paid increasing attention[39,40]. However, Bardel *et al*[41] argued that Treg cells did not express enough IL-35 in human, while recent studies have shown that IL-35 is enough to be detected in CD4+ T cells from peripheral blood of CHB patients and is negatively involved in the pathogenesis of HBVLF and LC[42,43].

Many studies have proved that Treg cells are significantly correlated with HBV infection and degree of liver fibrosis[44-48]. Treg cells increase with the number of HBV antigens and serve as a shelter for HBV to avoid immune attack as a result of immunosuppressive function[44], while the same immunosuppressive function can alleviate liver injury[45]. Simultaneously, increased Treg cells inhibit HSCs activation and proliferation, thus improving liver fibrosis[46,47]. However, the specific process of Treg cells in HBVLF remains to be elucidated; in particular, the increasing evidence that Treg cells can convert to effector T cells adds complexity of their roles[49,50].

***Th9, Th22 and Tfh cells***

In the presence of high levels of TGF-β and IL-4, naïve CD4+T cells convert to Th9 cells, which produce specific cytokine IL-9[51]. As a new subset of CD4+T cells, Th9 has been mainly studied in allergic inflammation, autoimmune disease and anti-tumor immunity[52], and their role in liver injury has been poorly investigated.

Th22 cells predominantly produce IL-22, and are differentiated from naïve CD4+ T cells in the condition of IL-6 and TNF-α[53]. Newly, Th22 cells and intrahepatic IL-22 have been reported to have hepatoprotective effects in drug-induced hepatocellular injury[54]. However, their roles in HBVLF are still poorly reported. Besides, the exact roles of Th22 cells are uncertain since IL-22 is also derived from other cells, especially Th17 cells.

Tfh cells continuously express high levels of Chemokine (C-X-C) receptor 5 and surface molecules such as inducible co-stimulator (ICOS), programmed cell-death protein (PD)-1, and CD40 ligand (CD40L)[55]. Expression of these surface molecules and cytokines IL-4 and IL-21 allows Tfh cells to have immunoregulatory function on T and B cells. Recently, significantly decreased circulating Tfh cells and impaired function of IL-21 production and B cell-maturation were found in HCC patients compared with HBV-related LC patients and healthy controls[56]. This suggests that impairment of Tfh cells may negatively involve in the progression of HBV-associated HCC, but data elucidating their relationship with liver fibrosis are still limited.

**HOMEOSTASIS OF TREG AND TH17 CELLS IN HBVLF**

Given the highly correlated roles of specific CD4+T subsets such as Th1, Th2, Th17 and Treg cells in HBV-related chronic hepatitis and fibrosis, and the interaction between them, current studies mainly focus on those subsets and their homeostasis, of which Treg and Th17 cells are the most intensively studied during HBVLF.

***Significance of the balance between Treg and Th17 cells during HBVLF***

As discussed above, Treg and Th17 cells are two important CD4+ T subsets that are developmentally highly correlated and functionally reciprocal during inflammation. Recent reports have proved their close interactions and transitions. Thus, there is a balance between Treg and Th17 cells.

In our previous work, we highlighted the significance of the balance between Treg and Th17 cells in the progression of HBVLF[3]. The ratio Treg/Th17, on behave of the balance, was negatively related to the severity of liver fibrosis[3]. Other researchers have also shown this phenomenon in patients with HBV-related LC and mouse models of liver fibrosis[46,47]. An imbalance of Th17 cell-dominant is closely correlated with liver fibrosis[3,46,47]. In addition, an imbalance was also reported in HBV-related ACLF, and liver injury was alleviated when the imbalance was restored[57-59]. Besides, some researchers found the improved liver function after transplantation of autologous bone marrow mesenchymal stem cells might be mediated through regulating Treg/Th17[60]. Therefore, the balance between Treg and Th17 cells is not only of great significance in indicating the severity of liver injury, but also has potential therapeutic value.

***Mechanisms of the balance between Treg and Th17 cells regulating liver fibrosis***

Recently, a growing number of studies have investigated the underlying mechanisms about how this Treg/Th17 balance regulates the process of liver fibrosis. In our previous work, when exogenous CD4+CD25- cells co-cultured with HSCs in contact manner, administration of anti-IL-17 antibody down-regulated, while addition of recombinant IL-17 significantly upregulated HSCs proliferation and pro-fibrotic cytokines production[3]. Whereas CD4+CD25+ Treg cells directly down-regulated the pro-fibrotic features of HSCs, which might be mediated through cell contact rather than the release of TGF-β or IL-10, and indirectly influence HSCs via inhibiting the Th17 response[3]. Other researchers have also found the imbalance of Treg/Th17 to Th17 dominance could activate HSCs in CCl4-treated mice with liver fibrosis[46]. Although these studies have demonstrated the crucial effects of the balance of Treg/Th17 on liver fibrosis through its impact on HSCs, whether there are other mechanisms remains to be elucidated.

***Regulation of the balance between Treg and Th17 cells***

The balance between Treg and Th17 cells is important in the pathogenic process of HBVLF, many studies have investigated factors that regulate their balance in order to achieve better clinical outcomes.

From the perspective of developmental pathways, TGF-β might be the first candidate for consideration. High concentration TGF-β induces FoxP3 and drives the differentiation of Treg cells[34]. While TGF-β plus IL-6 or IL-21 induce RORγt or signal transducer and activator of transcription (STAT)3, thus promoting Th17 development[21]. Although several researchers have indicated that TGF-β was not indispensable for the differentiation of Th17 cells[19,20], the modulatory effect of TGF-β cannot be ignored.

IL-21 suppresses FoxP3 gene transcription and promotes Th17 through regulating TGF-β signaling[21,61]. Vitamin A metabolite retinoic acid acts as a key regulator of TGF-β–dependent differentiation of Treg cells, and inhibits Th17 cell differentiation via directly counteracting the activity of IL-6[62]. IL-2, together with TGF-β, can drive Treg differentiation, whereas IL-2 also inhibit Th17 differentiation through a STAT5-dependent pathway[63].

Interactions between Treg and Th17 cells directly affect their balance. During HBV infection, Treg cells show an inhibitory effect on Th17 cells, which may due to the cytotoxicity of Treg cells or through inhibitory cytokines such as IL-10, TGF-β or IL-35[42,64,65]. Depletion of Treg cells enhances Th17 response, leading to more severe liver damage[3,64,65]. CD39+ Treg cells are a subset of CD4+Foxp3+ Treg cells, and have been reported to act as an effective factor in limiting Th17 cell-response[66].

However, there is accumulating evidence that Treg cells also upregulate the production of Th17-associated proinflammatory cytokines, referring mainly to IL-17 and IL-22[67,68]. The TNF–TNFR2 pathway might play a part in this phenomenon[69]. Zhao *et al*[69] have found that Treg cells deficient in TNFR2 support lower production of IL-17A (also called IL-17) and TNF by co-transferred Th17 cells. Furthermore, in their research, exogenous generated Th17 cells supported the expansion and phenotypic stability of CD4+Foxp3+ Treg cells *in vivo* via the same TNF–TNFR2 pathway[69]. Although the effects of Th17 cells on Treg cells are poorly discussed in liver injury, the bidirectional interactions between Treg and Th17 cells should be taken into consideration when concerning their homeostasis.

The plasticity of Treg and Th17 cells also shifts the balance between them. The stability of Treg cells is openly discussed[70]. However, much evidence shown that Treg cells secrete IL-17 when activated under certain conditions, for example, under the stimulation of Toll-like receptor (TLR)2, TLR4 or TLR9 and Th17-biasing cytokine conditions such as IL-6, IL-21, IL-23 and IL-1β[71-75]. Simultaneously, these IL-17-producing Treg cells retain expression of FoxP3 but lose suppressive function when secrete IL-17[71]. However,the lost suppressive function can recover *in vitro*[71,72]. Whether the ability to secrete IL-17 by Tregcells can be regarded as plasticity or an adaptive response remains to be elucidated, but the discovery of IL-17-producing FoxP3+ cells supports an additional mechanism of the balance between Treg and Th17 cells.

Unlike Treg cells, the plasticity of Th17 cells is widely reported. During chronic inflammation, Th17 cells can convert to Th1 or Th2 cells[32,33]. Of note, in the presence of IL-12 and TNF-α, Th17 cells rapidly shift towards an IFN-γ-producing Th1 phenotype, and lose the ability for IL-17-production[76,77]. Intriguingly, Ye *et al*[78] have reported that human tumor-infiltrating Th17 cells separated from melanoma, ovarian, breast and colon cancers, can differentiate into FoxP3+ cells due to T-cell receptor stimulation and subsequent epigenetic modification and gene reprogramming. In their studies, the tumor-infiltrating, Th17-derived, FoxP3+ Treg cells still had potent suppressive function, but they could not reconvert back to Th17 cells under Th17-biasing cytokine conditions[78]. Their results indicate another substantial plasticity of Th17 cells, whether this can be extended to other microenvironments remains to be determined.

**IMPLICATIONS FOR TREATMENT STRATEGIES OF HBVLF**

Recent treatment strategies for chronic HBV infection mainly aim at targeting the virus directly or restoring an effective immune response. As for the process of HBVLF, the inappropriate immune response induced by CD4+T cells is of great help. So, treatment strategies aim at mitigating or even eliminating the progression of inflammation and fibrosis can concentrate on restoring the homeostasis of CD4+ T cells, of which the balance between Treg and Th17 cells is the most important. Any factors that achieve a positive anti-fibrotic effect or a decreased pro-fibrotic effect targeting Treg and Th17 cells has potential therapeutic value for chronic HBV-induced liver injury. As described above, this can be obtained in different ways: from the perspective of development pathways, on the level of function, or by regulating their conversion. Here, we mainly concentrate on the level of function, including interleukins associated with Treg or Th17 cells, or both (see table 1) and some surface molecules (see table 2) that regulate the homeostasis of CD4+ T cells.

***Interleukins associated with Treg and Th17 cells***

**IL-17A:** IL-17A is the dominating cytokine of Th17-associated cytokines. As discussed above, expression of IL-17A is positively related to hepatitis and the increasing severity of liver fibrosis. Targeting of IL-17A has yielded good results in animal models. In our previous work, in ConA-treated mice, blockade of IL-17A using anti-IL-17 monoclonal antibody markedly down-regulated expression of α-smooth muscle actin and decreased serum alanine aminotransferase (ALT) level, thus alleviating liver injury and fibrosis[3]. In CCl4–treated mice, Sun *et al*[17] observed decreased proinflammatory cytokines, reduced neutrophil recruitment, and less hepatocellular necrosis in IL-17A receptor (IL-17AR)-deficient mice. Meng *et al*[16] also reported that liver fibrosis induced by either bile duct ligation (BDL) or CCl4 was alleviated in IL-17AR deletion mice. Moreover, Zheng *et al*[79] found that most patients with HBV-related decompensated cirrhosis who undergone bone marrow-derived stem cells (BMSCs) transplantation displayed significantly improved liver function, which was at least partly through down-regulating IL-17.

**IL-21/23:** IL-21 is important in initiating and amplifying differentiation of Th17 cells[18,21]. Korn *et al* observed that Th17 cell-frequencies in IL-21 receptor-deficientT cells was half that of wild-type T cells in the condition of IL-6 and TGF-β[21]. They also indicated that IL-21 was one of the most efficient alternative cytokines in inhibiting TGF-β-driven FoxP3+ Treg induction in IL-6-deficient mice[21]. As another indispensable factor for Th17 differentiation, IL-23 promote Th17 cell-proliferation and stabilize final funtional Th17 cells, and IL-23 or IL-23 receptor-deficient cells failed to stimulate enough functional IL-17-producing cells[22]. During HBV infection, Wang *et al* observed high expression of IL-23 and IL-23 receptor in CHB and ACLF patients, and *in vitro* IL-23-blocking antibody significantly decreased the production of IL-17[80]. Accordingly, they emphasized the importance of the IL-23/Th17 axis in HBV-related liver damage[80].

**IL-22:** The context-dependent pro- and anti-inflammatory nature of IL-22 has been described under different conditions of liver diseases[23-26]. Although several studies showed that administration of IL-22 ameliorated liver fibrosis in different mouse models, Zhao *et al* pointed out that those models had differences from HBV-induced immune-mediated liver fibrosis[26]. In their HBV-transgenic mice, they observed that blockade of IL-22 reduced Th17 cell-recruitment and ameliorated liver inflammation and fibrosis *in vivo* and *in vitro*[26]. In another HBV-transgenic mouse model, Zhang *et al* found that the severity of subsequent liver injury was alleviated by neutralization of IL-22 when splenocytes were transferred from HBV-immunized mice[23]. And they indicated that this effect was not dependent on HBV inhibition, but rather inhibited the recruitment of all leukocyte subsets into the liver and reduced intrahepatic chemokine expression[23]. Inverse effects that IL-22 exhibits in different etiology-induced immune microenvironments need to be clarified in future studies and may be of significance for the development of new therapeutic approaches.

**IL-10:** IL-10 is an important multi-sourced, anti-inflammatory cytokine[35]. In the liver, IL-10 can be produced by hepatocytes, Kupffer cells, HSCs, regulatory B (Breg) cells, and Treg cells[81]. As mentioned above, IL-10 can inhibit Th1, Th2 and Th17 responses as well as restrain activation of HSCs[38]. In CCl4-treated mice, deletion of IL-10 gene resulted in significantly more severe fibrosis[82]. In addition, in thioacetamide (TAA)-treated mice, exogenous administration of IL-10 gene reversed already established hepatic fibrosis[83]. Taken together, IL-10 might have potential for future treatment of HBV infection and liver fibrosis. Meanwhile, since IL-10 has broad biological effects, future studies should pay more attention to decreasing its side effects.

**IL-35:** IL-35 is identified as a novel immunosuppressive cytokine produced by Treg and Breg cells, and there is an increasing focus on its therapeutic utilities[39,40,84]. Recent studies showed that IL-35 was negatively involved in the pathogenesis of HBVLF and cirrhosis[42]. However, studies of the association between IL-35 and chronic HBV infection are still limited. Nowadays, IL-35 is mainly investigated in autoimmune diseases. One study on primary biliary cirrhosis has suggested that in dominant-negative TGF-β receptor type II mice, deletion of gene encoding the IL-12p35 subunit, which caused the absence of IL-12 and IL-35, promoted Th17 response and liver fibrosis, as well as inhibit Th1 response[85]. This results suggested that IL-35 might be closely associated with liver fibrosis.

**IL-33:** IL-33 belongs to the IL-1 family, and it has close correlation with liver injury and fibrosis in chronic hepatitis[86,87]. In the liver, the major source of intrahepatic IL-33 is LSECs and activated HSCs[87]. Through soluble receptor ST2, IL-33 promotes Th2 response and increases production of Th2 cytokines (IL-4, IL-5 and IL-13) *in vitro* and *in vivo*[86-88]. However, some researchers have provided evidence that the IL-33/ST2 axis can ameliorate liver inflammation[89,90]. In mice with ConA-induced liver injury, administration of IL-33 attenuated hepatitis, while mice with deficient ST2 developed significantly more severe hepatitis[89,90]. Zhao *et al*[91] have also found that IL-33 might activate Tfh cells, which facilitate humoral immunity to against HBV. The specific roles of IL-33 need to be further investigated, and it would be interesting to study the influence of IL-33 on different CD4+ T subsets in more detail.

***Surface molecules on CD4+ T cells***

Upregulated expression of surface co-inhibitory molecules, including PD-1, cytotoxic T lymphocyte-associated antigen-4 (CTLA)-4, T-cell immunoglobulin domain and mucin domain-containing molecule-3 (TIM)-3, lymphocyte activation gene-3, and CD244, can result in HBV-specific T cell exhaustion, which is a crucial mechanism in deviation of homeostasis of adaptive immunity and consequent persistence and progression of HBV infection[92,93]. These co-inhibitory molecules interact with corresponding ligands expressed on APCs, then deliver negative second activation signals, which decrease HBV-specific T-cell proliferation and cytokine production[93]. Studies mainly focus on CD8+-exhausted T cells during chronic HBV infection, but recently more attention has been paid to CD4+-exhausted T cells in consideration of their pivotal roles in cell immunity[94]. Furthermore, important role of these co-inhibitory molecules expressed on CD4+ T cells was identified in other chronic viral infection such as hepatitis C[95].

**PD-1:** PD-1 is a member of the CD28 superfamily, and exerts a wide range of immunoregulatory roles in T-cell activation and tolerance through binding to its ligands PD-L1 or PD-L2[96]. Some studies have described that the high expression levels of PD-1 on CD4+ T cells are strongly linked to exhaustion of HBV-specific CD4+ T cells[93,97,98]. Establishing one newly DRB1\*01-restricted (MHC class II) tetramer, Raziorrouh *et al* found that CD4+ T cells had elevated PD-1 expression, and PD-L1/PD-L2 neutralization reactivated CD4+T-cell proliferation and partially increased CD4+ T-cell production of IFN-γ, IL-2 and TNF-α[98]. Notably, in their study, four of thirteen patients who achieved long-term HBV suppression responded to PD-1 blockade, while the other nine with highly viral load failed to revive T-cell proliferation[98]. Raziorrouh *et al*[95] also found blockade of PD-L1/PD-L2 increased frequencies of HCV-specific CD4+ T cells, promoted CD4+ T-cell expansion and production of IFN-γ and TNF-α, while influenza- and Epstein-Barr virus-specific CD4+T cells did not respond significantly to any *in vitro* blockade. The responses of CD4+ T cells to the blockade of PD-1 may differ from viral load and different chronic virus infection. Besides, limited data elucidate the relationship between PD-1 expression and progression of chronic HBV infection. Wang *et al* reported that although PD-1 expression was upregulated in LC and HCC, the upregulation was small and there was no significant difference between PD-1 and the severity of liver injury[97]. PD-1 expressed on CD4+ T cells in chronic HBV infection and related liver fibrosis need further researched.

**TIM-3:** TIM-3, which is expressed on CD4+ and CD8+ T cells, negatively regulates T-cell responses and induces tolerance through binding to its ligand galectin-9[99,100]. The Tim-3/galectin-9 pathway is also essential for the homeostasis of Treg cells[100,101]. Recent researches have indicated that expression of Tim-3 on CD4+ T cells is upregulated in patients with CHB compared to health controls, and is positively associated with the severity of HBV infection[93,102]. Besides, the level of Tim-3 is decreased after antiviral treatment[102]. However, Raziorrouh *et al*[98] observed persistent low level of TIM-3 in CHB patients and TIM-3 single blockade had little influence on CD4+T-cell function. This difference might be due to the relative paucity of CD4+ T cells and the DRB1\*01-restricted MHC class II tetramer used, in which DRB1\*01+CD4+ T cells were only specific to HBV core epitope 61–80. In a recent study of mice with chronic lymphocytic choriomeningitis virus (LCMV) infection, treatment with vinegar-processed floss of *Daphne genkwa*, one traditional folk medicine extract, showed functional restoration of exhausted LCMV-specific CD4+ and CD8+ T cells, and this restoration might because of the down-regulating PD-1 and Tim-3 expressions[103]. Moreover, it has been reported that targeting both PD-1 and Tim-3 is an effective immune strategy to restore exhausted CD8+ T cells during chronic viral infection[104]. Future studies could pay more attention to the blockade of both TIM-3 and PD-1 pathways on HBV-specific CD4+ T cells.

**CTLA-4:** CTLA-4 is expressed on activated and regulatory CD4+T cells to limit their over-activation and maintain tolerance[105]. It is widely reported that CTLA-4 has close correlation with HBV infection in regulating Th1/Th2 cytokine production toward Th2 responses[106-108]. Besides, some researchers have indicated that CTLA-4 gene polymorphism might be associated with HBV progression and viral persistence[107,109]. However, expression of CTLA-4 on specific CD4+ T cells in chronic HBV infection is still obscure. Recent years have witnessed prominent effects of CTLA-4 blocking. CTLA-4 blockade with its monoclonal antibody *tremelimumab* has been tested in patients with HCC and HCV-induced LC, and *tremelimumab* has good antitumor and antiviral effects[110]. In Propionibacterium acnes (P. acnes) and lipopolysaccharide (LPS)-induced mouse models of fulminant hepatitis, most of the mice not injected with adenovirus encoding CTLA-4 immunoglobulin (AdCTLA-4-Ig) died while all treated mice survived, suggesting that CTLA-4-Ig could be useful for treatment of severe liver injury[111]. All of that indicates the importance of CTLA-4 in chronic viral infection and progression. Future studies could investigate in-depth its correlation with the homeostasis of HBV-specific CD4+ T cells.

**Cannabinoid receptor 2:** Other than these co-inhibitory molecules on the surface of CD4+T cells, surface receptors such as cannabinoid receptor 2 (CB2) have also received attention because of their anti-inflammatory and anti-fibrotic properties in mouse liver[112]. CB2 is abundantly expressed in almost all immune cells[113]. In BDL-treated CB2-/- mice, intrahepatic Th17 and IL-17 production were increased, while using CB2 agonist JWH-133 *in vitro*, the differentiation and functions of Th17 cells were decreased[112]. In CCl4-treated CB2-/- mice, JWH-133 displayed an additional potent hepatoprotective property[114]. Thus, activating CB2 on Th17 cells may be effective in future therapy of liver fibrosis. And it may be interesting to investigate the relation of CB2 with HBV infection and subsequent diseases.

**CONCLUSION**

HBVLF is an intricate disease process that cannot be regulated by a single cytokine or immune cell. From the perspective of CD4+ T cells, the disequilibrium of these cells contributes a lot as discussed, and restoring homeostasis may be of great help to reestablish effective immunity against HBV-related pathological processes. However, there are still a lot of problems to be resolved. First, the specific regulation mechanisms of CD4+ T-cell homeostasis, especially the balance of Treg and Th17 cells are still not fully elucidated in the process of HBV-induced liver injury. Second, the practical situations are not always as good as in theory, and naturally developing HBV–specific immunity in CHB patients may not be the same as that in mouse models. Moreover, how to apply current findings from mice to humans with good therapeutic effects and few side effects is worthy of further research constantly.

There is still a long way to go in the restoration of homeostasis of CD4+ T cells in HBVLF, but it will be meaningful in elucidating the pathogenesis and resistance of chronic HBV infection. It is noteworthy that the homeostasis of CD4+ T cells is only part of the immunoregulatory network. We should be concerned with the local regulation of themselves, as well as their interactions with other areas, especially their links with innate immunity. For instance, in our previous work, we found that the fibrotic factor high-mobility group box (HMGB)1, one of the damage-associated molecular pattern molecules, could transmit signals from necrotic cells to innate immune cells and then pass on to CD4+ T cells through the axis of HMGB1–TLR4-IL-6–Treg/Th17 balance in CHB patients[115]. As a result, HMGB1 favors Th17 responses but inhibits Treg responses, thus exerting proinflammatory and pro-fibrotic effects[115]. Therefore, future studies should also take innate immunity seriously when considering the homeostasis of CD4+ T cells.

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**Table 1 Role of Treg and Th17 cell-related interleukins in chronic hepatitis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treg and Th17-related interleukins** | **Cellular sources**  | **Role in CD4+ T cell differentiation and function** | **Role in liver inflammation and fibrosis** | **Referrences** |
| IL-17 | **Th17**, neutrophils, NKT cells, macrophages, γδT cells | Specific cytokine of Th17 cells: proinflammatory | Proinflammatory;Pro-fibrotic | [6-8,10,31] |
| IL-21 | **Th17**, **Tfh**, NKT cells | Promote the differentiation of Th17 cells;Inhibit the differentiation of Treg cells | Promote HBV-related liver injury;Promote fibrogenesis | [18,21,28-30] |
| IL-23 | DC, macrophages | Promote Th17 cell-proliferation and stabilize effector Th17 cells | Promote HBV-related liver injury | [22,80] |
| IL-22 | **Th17**, **Th22**, activated NK, NKT cells | Specific cytokine of Th22 cells: proinflammatory | Hepatoprotective? Proinflammatory? Pro-fibrotic? Anti-fibrotic? | [23,24,26,27] |
| IL-10 | **Treg**, hepatocytes, Kupffer cells, LSECs, HSCs, Breg | Inhibit Th1, Th2, Th17 differentiation and cytokine production | Anti-inflammatory;Anti-fibrotic | [35,38,81] |
| IL-35 | **Treg**, Breg | one cytokine produced by Treg cells: immunosuppressive | Anti-inflammatory;Anti-fibrotic? | [30,31,33,34] |
| IL-33 | LSECs, activated HSCs | Promote Th2 differentiation and cytokine production;Increase Treg cells?Activate Tfh cells? | Pro-fibrotic;Anti-inflammatory? | [86-88,90,91] |

Treg: Regulatory T; Th: T helper; Tfh: T follicular helper; IL: Interleukin; HBV: Hepatitis B virus**;** NK: Natural killer; DC: Dendritic cells; LSECs: Liver sinusoidal endothelial cells; HSCs: Hepatic stellate cells.

**Table 2 Role of surface molecules in chronic hepatitis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Surface molecules** | **Expression on T cells and specific CD4+ T-cell subsets** | **General effects**  | **Role in liver inflammation and fibrosis** | **CD4+ T-cell response to blocking** | **References** |
| PD-1 | CD8+ T, CD4+ T | Inhibit T cell activation;Maintain tolerance | Result in the exhaustion of HBV-specific CD8+ and CD4+ T cells | Partially revive the proliferation and function of HBV-specific CD4+ T cells  | [96-98,104] |
| TIM-3 | CD8+ T, CD4+ T; **Treg** | Inhibit T cell activation;Maintain tolerance | Promote progression of HBV infection | Revive more together with PD-1 blocking | [99,100,102-104] |
|  CTLA-4 | activated CD4+ T; **Treg** | Inhibit CD4+ T cell-overactivation;Maintain tolerance | Promote persistence of HBV and progression of HBV infection;  | Not sure | [105,107,109,110] |
| CB2  | CD4+ T, CD8+ T; **Th17** | Immunoregulatory: proinflammatory or anti-inflammatory;Anti-fibrotic | Anti-inflammatory;Anti-fibrotic;Hepatoprotective? | Decrease the frequency and function of Th17 cells | [112-114] |

PD-1: Programmed cell-death protein; CTLA-4: Cytotoxic T lymphocyte-associated antigen; TIM-3: T-cell immunoglobulin domain and mucin domain-containing molecule; CB2: Cannabinoid receptor 2; Treg: Regulatory T; Th: T helper.