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TOPIC HIGHLIGHT

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

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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 and hepatocellular carcinoma. 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 liver cirrhosis. Therefore, defining 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 emphasize $CD4^+$ T-cell homeostasis and the important balance between regulatory T (Treg) and T helper 17 (Th17) cells. 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 surface molecules such as programmed cell death protein 1, cytotoxic T lymphocyte-associated antigen 4, T cell immunoglobulin domain and mucin domain-containing molecule 3 and cannabinoid receptor 2 that have potential therapeutic implications for 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

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) cells and T helper 17 (Th17) cells is pivotal in HBVLF. Therefore, uncovering the underlying mechanisms of $CD4^+$ T cell homeostasis regulating

HBVLF may help achieve better clinical outcomes. We discuss Treg and Th17 cell-related cytokines and surface molecules that may be targeted therapeutically to alter CD4$^+$ T-cell homeostasis in chronic HBV infection.

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INTRODUCTION

Over 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. HBV is hepatotropic but not cytopathic, and interactions between HBV, hepatocytes and the host immune system determine the natural history of infected individuals[1]. CD4$^+$ T cells play key roles in HBV infection. On one hand, CD4$^+$ T cells substantially impact the clearance of HBV by aiding cytotoxic CD8$^+$ T cells, B cells and natural killer T cells[2]. On the other hand, CD4$^+$ T cells contribute to the pathogenesis of inflammation progression *via* production of an array of pro-inflammatory and pro-fibrotic cytokines[2,3].

Liver fibrosis is recognized as a wound-healing response driven primarily by inflammation in response to various parenchymal injuries[4]. HBV-related liver fibrosis (HBVLF) is a reversible, intermediate stage of chronic hepatitis B (CHB) and LC[5]. As conventional subsets of CD4$^+$ T cells, T helper 1 (Th1) and Th2 cells are well-known. Th1 cells produce high levels of interferon γ (IFN-γ), which helps to develop an efficient, specific antiviral immune response and attenuate tissue fibrosis[6,7]. Th2 cells produce interleukin (IL)-4, IL-5 and IL-13, which suppress Th1 cells, resulting in persistent HBV replication and chronic liver immunopathology, and are directly involved in fibrogenesis[6-8]. However, detailed study of the immunity of liver fibrosis has shown that the Th1/Th2 dichotomy is not appropriate. Nowadays, the crucial roles of newly-identified CD4$^+$ T-cell subsets are widely recognized and extensively researched in the progression of CHB.

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

On the basis of characteristic transcription factors, unique cytokine profiles and discrete functional properties, CD4$^+$ T cells can be subdivided into new subsets. These include Th17, Th9, Th22, T follicular helper (Tfh) and regulatory T (Treg) cells, in addition to the conventional Th1 and Th2 cells.

Th17 cells

IL-17 and its potential role in immunity were discovered two decades ago[9], then Th17 cells were defined as an independent lineage of T-helper cells in 2005[10,11]. Since then, IL-17 and Th17 cells have been extensively studied to define their properties and roles. At present, the pathogenic role of Th17 cells in promoting liver injury and fibrosis is widely recognized[12-15]. Circulating and intrahepatic Th17 cell numbers are increased in HBV-infected patients with CHB or HBV-related acute-on-chronic liver failure (ACLF), and IL-17 expressions positively related to the severity of liver injury and inflammation progression[12,13]. Th17 cell numbers also increase with the severity of liver fibrosis in humans and mice[14,15].

Until now, the role of Th17 cells in the pathogenesis of liver fibrosis has not yet been fully elucidated. Several studies have found that IL-17 affects hepatic stellate cells (HSCs), by recruiting neutrophils and monocytes[14-17]. However, the whole is greater than the sum of its parts. When naïve CD4$^+$ T cells are exposed to transforming growth factor (TGF)-β and IL-6 during antigen activation, the cells upregulate the Th17 cell-specific transcriptional factor retinoid orphan nuclear receptor γt (RORγt) and differentiate into Th17 cells[10,11]. In addition, 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 function of Th17 cells[18-22]. After activation, Th17 cells secrete a mixture of cytokines including IL-17, IL-21, IL-22, IL-6, IL-9 and tumor necrosis factor α (TNF-α). Although most Th17 cell-mediated pathogenic effects are attributed to IL-17, the impact of Th17 cells is more complex than IL-17-mediated effects.

IL-22 is produced primarily by Th17 cells, and exerts hepatoprotective or pathological effects under different settings of liver diseases, such as acute liver damage induced by carbon tetrachloride (CCl_4), concanavalin A or Fas ligand, alcoholic liver diseases, and chronic hepatitis caused by HBV or hepatitis C virus (HCV) infection[23-26]. Zhao *et al*[26] found that IL-22 was positively related to hepatitis and fibrosis in HBV-infected patients with LC, and using an HBV transgenic mouse model, the authors suggested that IL-22 exacerbated chronic hepatitis and fibrosis by promoting Th17 cell recruitment[26]. Other researchers have noted that the predominance of IL-22's pathological functions over its protective functions in patients with HBV was due to the cytokine's ability to upregulate chemokine expression to recruit inflammatory cells into the liver[23]. However, there are also some researchers have observed that the levels of IL-22 were significantly reduced in severe liver injuries during CHB[27].

Another important Th17 cell-related cytokine is IL-21. Recent studies have indicated that both

circulating IL-21$^+$CD3$^+$CD8$^-$ T cell numbers and intrahepatic IL-21 levels are correlated with the severity of liver damage in patients with active CHB, HBV-related LC and HBV-related ACLF[28-30]. In addition, IL-21 causes HSC activation *in vitro*, thus facilitating the fibrogenesis of LC[29].

The effects of Th17 cells in 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 Th17-related cytokines, other sources of these cytokines [such as IL-17 produced by neutrophils, natural killer T (NKT) cells, macrophages, and γδT cells] may make it difficult to define the exact roles of Th17 cells in liver fibrosis[31]. In recent years, the plasticity of Th17 cells during inflammation has been widely reported[32,33], revealing the importance of crosstalk between different CD4$^+$ T-cell subsets.

Treg cells

CD4$^+$CD25$^+$ Treg cells are a lineage of CD4$^+$ T cells characterized by production of TGF-β and expression of the transcription factor Forkhead box P3 (FoxP3)[34]. Treg cells exhibit immunosuppressive and self-tolerant functions by direct cell contact and by secreting inhibitory cytokines such as IL-10, TGF-β and IL-35.

IL-10 can inhibit Th1 and Th2 cell responses through antigen-presenting cells[35]. IL-10 can also prevent the induction of Th17 cell responses, but cannot suppress an established Th17 cell-mediated chronic inflammation[36]. During HBV-related disease progression, IL-10 may serve as a negative feedback mechanism to regulate pro-inflammatory Th17 cell responses[37]. Moreover, activated HSCs produce IL-10, which constrains the cells' ability to produce collagen, thereby blocking the progression of liver fibrosis[38].

IL-35 is a novel inhibitory cytokine produced by Treg cells, and has been receiving increasing attention[39,40]. However, Bardel *et al*[41] argued that Treg cells do not express sufficient levels of IL-35 in humans. Recent studies have shown that IL-35 can be detected in circulating CD4$^+$ T cells from CHB patients and can inhibit the pathogenesis of HBVLF and LC[42,43].

Many studies have shown that Treg cells are significantly correlated with HBV infection and the degree of liver fibrosis[44-48]. Treg cell numbers increase with the number of HBV antigens. The virus also uses the cells for shelter, avoiding immune attack due to the cells' immunosuppressive activities[44], while the same immunosuppressive function works on other cell types to alleviate liver injury[45]. Simultaneously, Treg cells inhibit HSC activation and proliferation, thus limiting liver fibrosis[46,47]. However, the specific actions of Treg cells in HBVLF remain to be elucidated; in particular, the increasing evidence that Treg cells can convert to effector T cells adds complexity to the situation[49,50].

Th9, Th22 and Tfh cells

In the presence of high levels of TGF-β and IL-4, naïve CD4$^+$ T cells differentiate to Th9 cells, which produce IL-9[51]. As a newly-identified subset of CD4$^+$ T cells, Th9 cells have been studied only in allergic inflammation, autoimmune disease and tumor immunity[52]; the role of Th9 cells in liver injury is unknown.

Th22 cells predominantly produce IL-22, and develop from naïve CD4$^+$ T cells in the presence of IL-6 and TNF-α[53]. Th22 cells and intrahepatic IL-22 have been reported to have hepatoprotective effects in drug-induced hepatocellular injury[54]. However, the role of Th22 cells and IL-22 in HBVLF is unknown. Defining this role may be challenging, since IL-22 is also produced by other cells, especially Th17 cells.

Tfh cells express high levels of chemokine receptor 5, inducible co-stimulator, programmed cell death protein1 (PD-1), and CD40L[55]. Expression of these surface molecules, along with cytokines IL-4 and IL-21, allows Tfh cells to regulate T cells and B cells. Recently, HCC patients were found to have significantly fewer circulating Tfh cells with impaired IL-21 production and B cell regulatory properties, compared with HBV-infected LC patients and healthy controls[56]. This suggests that Tfh cells may negatively involve in the progression of HBV-associated HCC, but the role of Tfh cells in liver fibrosis is unknown.

HOMEOSTASIS OF TREG AND TH17 CELLS IN HBVLF

Given the specific roles of Th1, Th2, Th17 and Treg cells in HBV-related chronic hepatitis and fibrosis, and the way these subsets affect each other, current studies mainly focus on the subsets and their homeostasis. Treg and Th17 cells are the most intensively studied subsets for HBVLF.

Significance of the balance between Treg and Th17 cells during HBVLF

As discussed above, Treg and Th17 cells are important CD4$^+$ T cell subsets that are developmentally 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]. We found that the ratio Treg/Th17 was negatively related to the severity of liver fibrosis[3]. Other researchers found this correlation in patients with HBV-related LC and mouse models of liver fibrosis[46,47]. A dominance of Th17 cells is closely correlated with liver fibrosis[3,46,47]. In addition, an imbalance in the ratio was reported in HBV-related ACLF, and liver injury was alleviated when the balance was restored[57-59]. Several groups found that improved liver function after transplantation of autologous bone marrow mesenchymal stem cells might be mediated by changes in the Treg/Th17 ratio[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 where by the Treg/Th17 balance regulates the process of liver fibrosis. When CD4$^+$CD25$^-$ cells were co-cultured with HSCs, an anti-IL-17 antibody down-regulated - and recombinant IL-17 upregulated - HSC proliferation and pro-fibrotic cytokine production[3]. Using a transwell co-culture system, we found that CD4$^+$CD25$^+$ Treg cells directly down-regulated the pro-fibrotic features of HSCs by cell contact rather than through the release of TGF-β or IL-10[3]. Other researchers found that a Th17 cell dominance over Treg cells could activate HSCs in CCl_4-treated mice with liver fibrosis[46]. Although these studies have demonstrated the crucial effects of the Treg/Th17 balance on liver fibrosis through an impact on HSCs, whether there are other mechanisms remains to be elucidated.

Regulation of the balance between Treg and Th17 cells

Because the balance between Treg and Th17 cells is important in the pathogenesis of HBVLF, many studies have investigated factors that regulate the Treg/Th17 balance in order to achieve better clinical outcomes.

From the perspective of developmental pathways, TGF-β might be the first candidate for consideration. High concentrations of TGF-β induce FoxP3 expression in naïve CD4$^+$ T cells, driving their differentiation into Treg cells[34]. In contrast, TGF-β plus IL-6 or IL-21 induce the expression of RORγt and signal transducer and activator of transcription 3 (STAT3), promoting Th17 cell differentiation[21]. Although several groups have indicated that TGF-β is dispensable for the differentiation of Th17 cells[19,20], the modulatory effect of TGF-β cannot be ignored.

IL-21 suppresses FoxP3 expression and promotes Th17 cell differentiation by regulating TGF-β signaling[21,61]. The vitamin A metabolite retinoic acid is a key regulator of TGF-β-mediated Treg cell differentiation and inhibits Th17 cell differentiation by directly counteracting the activity of IL-6[62]. IL-2, together with TGF-β, can drive Treg cell differentiation, and IL-2 inhibits Th17 cell differentiation through a STAT5-dependent pathway[63].

Interactions between Treg and Th17 cells directly affect their balance. During HBV infection, Treg cells inhibit Th17 cells, either through Treg cell cytotoxicity or through inhibitory cytokines such as IL-10, TGF-β or IL-35[42,64,65]. Depletion of Treg cells enhances Th17 cell responses, leading to more severe liver damage[3,64,65]. Treg cells expressing CD39 have been reported to effectively limit Th17 cell-responses[66].

However, there is accumulating evidence that Treg cells also upregulate the production of Th17 cell-associated pro-inflammatory cytokines, mainly IL-17 and IL-22[67,68]. The TNF-TNFR2 pathway might play a part in this phenomenon[69]. Zhou *et al*[69] found that Treg cells deficient in TNFR2 support lower production of IL-17A (also called IL-17) and TNF by co-cultured Th17 cells. Furthermore, the authors found that exogenously-generated Th17 cells supported the expansion and phenotypic stability of Treg cells *in vivo via* the same TNF-TNFR2 pathway[69]. Although the effects of Th17 cells on Treg cells are unclear in liver injury, the bidirectional interactions between Treg and Th17 cells likely affect their homeostasis.

The plasticity of Treg and Th17 cells also affects their balance. The stability of Treg cells is openly discussed[70]. However, multiple groups have shown that Treg cells secrete IL-17 when activated under certain conditions, for example, by Toll-like receptor 2 (TLR2), TLR4 or TLR9 and Th17-biasing cytokine conditions such as IL-6, IL-21, IL-23 or IL-1β[71-75]. These IL-17-producing Treg cells retain expression of FoxP3 but lose their suppressive functionality[71]. However, the lost suppressive function can recover *in vitro*[71,72]. Whether the ability to secrete IL-17 by Treg cells 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 maintaining 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]. Notably, in the presence of IL-12 and TNF-α, Th17 cells rapidly shift towards an IFN-γ-producing Th1 cell phenotype, and lose the capacity for IL-17-production[76,77]. Intriguingly, Ye *et al*[78] reported that human tumor-infiltrating Th17 cells from melanoma, ovarian, breast and colon cancers can express FoxP3 in response to T-cell receptor stimulation and subsequent epigenetic modification and gene reprogramming. In these studies, the FoxP3$^+$ cells derived from tumor-infiltrating Th17 cells had potent suppressive activity and did not convert back to Th17 cells under Th17 cell differentiation conditions[78]. These results provide another example of Th17 cell plasticity, although whether this Th17-to-Treg cell event occurs *in vivo* remains to be determined.

IMPLICATIONS FOR HBVLF TREATMENT STRATEGIES

Current treatment strategies for chronic HBV infection primarily target the virus directly or attempt to restore an effective antiviral immune response. As for the process of HBVLF, the inappropriate immune response induced by CD4$^+$ T cells is responsible for causing the disease. Treatment strategies aimed at mitigating or even eliminating the progression of inflammation and fibrosis can focus on the homeostasis of CD4$^+$ T cells,

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

Treg and Th17-related interleukins	Cellular sources	Roles in CD4$^+$ T cell differentiation and function	Roles in liver inflammation and fibrosis	Ref.
IL-17	Th17, neutrophils, NKT cells, macrophages, γδT cells	Characteristic cytokine of Th17 cells: pro-inflammatory	Pro-inflammatory Pro-fibrotic	[6-8,10,31]
IL-21	Th17, Tfh, NKT cells	Promotes differentiation of Th17 cells; Inhibits differentiation of Treg cells	Promotes HBV-related liver injury and fibrogenesis	[18,21,28-30]
IL-23	DCs, macrophages	Promotes Th17 cell proliferation and stabilizes effector Th17 cells	Promotes HBV-related liver injury	[22,80]
IL-22	Th17, Th22, activated NK and NKT cells	Characteristic cytokine of Th22 cells: pro-inflammatory	Hepatoprotective? Pro-inflammatory? Pro-fibrotic? Anti-fibrotic?	[23,24,26,27]
IL-10	Treg, hepatocytes, Kupffer cells, LSECs, HSCs, Breg	Inhibits Th1, Th2, Th17 cell differentiation and cytokine production	Anti-inflammatory Anti-fibrotic	[35,38,81]
IL-35	Treg, Breg	Immunosuppressive	Anti-inflammatory Anti-fibrotic?	[30,31,33,34]
IL-33	LSECs, activated HSCs	Promotes Th2 differentiation and cytokine production; Increases Treg cells? Activates Tfh cells?	Pro-fibrotic Anti-inflammatory?	[86-88,90,91]

Treg: Regulatory T cells; Tfh: T follicular helper cells; HBV: Hepatitis B virus; NK: Natural killer cells; NKT: Natural killer T cells; DCs: Dendritic cells; Breg: Regulatory B 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 CD4$^+$ T cell subsets	General effects	Role in liver inflammation and fibrosis	CD4$^+$ T cell response to blocking	Ref.
PD-1	CD8$^+$ T cells CD4$^+$ T cells	Inhibits T cell activation; Maintains tolerance	Causes exhaustion of HBV-specific CD8$^+$ and CD4$^+$ T cells	Partially-revived proliferation and function	[96-98,104]
TIM-3	CD8$^+$ T cells CD4$^+$ T cells Treg cells	Inhibits T cell activation; Maintains tolerance	Promotes progression of HBV infection	Revived more (blocked with PD-1)	[99,100,102-104]
CTLA-4	Activated CD4$^+$ T cells Treg cells	Inhibits CD4$^+$ T cell over-activation; Maintains tolerance	Promotes persistence of HBV and progression of HBV infection	Unknown	[105,107,109,110]
CB2	CD4$^+$ T cells CD8$^+$ T cells Th17 cells	Immunoregulatory: pro-inflammatory or anti-inflammatory; Anti-fibrotic	Anti-inflammatory; Anti-fibrotic; Hepatoprotective?	Decreased frequency and function of Th17 cells	[112-114]

PD-1: Programmed cell-death protein 1; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; TIM-3: T-cell immunoglobulin domain and mucin domain-containing molecule 3; CB2: Cannabinoid receptor 2; HBV: Hepatitis B virus.

in particular the balance between Treg and Th17 cells. Any treatment that achieves an anti-fibrotic effect by targeting Treg and/or Th17 cells has potential therapeutic value for chronic HBV-induced liver injury. As described above, the treatment can work in different ways: cell development, cell function, or cell conversion. In this section, we mainly concentrate on Treg/Th17 cell function, discussing the cytokines (Table 1) and surface molecules (Table 2) that regulate the homeostasis of CD4$^+$ T cells.

Interleukins associated with Treg and Th17 cells

IL-17A: IL-17A is the dominant member of Th17 cell-associated cytokines. As discussed above, IL-17A levels correlate positively with hepatitis and the severity of liver fibrosis. Targeting IL-17A has yielded substantial results in animal models. In our previous work with concanavalin A-treated mice, blockade of IL-17A using an anti-IL-17 monoclonal antibody markedly down-regulated the expression of α-smooth muscle actin and decreased the level of serum alanine aminotransferase (ALT), thus alleviating liver injury and fibrosis[3]. In addition, Tan *et al*[17] found that IL-17A receptor-deficient mice exhibited decreased pro-inflammatory cytokine levels, reduced neutrophil recruitment, and less hepatocellular necrosis in the CCl_4 model than did wild-type mice. Similarly, Meng *et al*[16] reported that liver fibrosis induced by either bile duct ligation or CCl_4 was reduced in IL-17AR-deficient mice. Zheng *et al*[79] found that most patients with HBV-related decompensated cirrhosis who underwent bone marrow-derived stem cell transplantation displayed significantly improved liver function, due in part to decreased levels of IL-17.

IL-21 and IL-23: IL-21 is important in initiating

and amplifying the differentiation of Th17 cells[18,21]. Korn *et al*[21] observed that Th17 cell-frequencies were reduced by 50% when IL-21 receptor-deficient T cells were cultured with IL-6 and TGF-β. The authors also indicated that IL-21 was one of the most efficient alternative cytokines to IL-6 in inhibiting TGF-β-driven FoxP3$^+$ Treg cell differentiation in IL-6-deficient mice[21]. Another indispensable factor for Th17 cell differentiation, IL-23 promotes Th17 cell proliferation and stabilizes Th17 cell function. IL-23- or IL-23 receptor-deficient cells failed to stimulate enough functional IL-17-producing cells[22]. Wang *et al*[80] observed high levels of IL-23 and IL-23 receptor in HBV-infected CHB and ACLF patients, and an IL-23 neutralizing antibody significantly decreased the production of IL-17 *in vitro*. Accordingly, the authors emphasized the importance of IL-23 and Th17 cells 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 ameliorates liver fibrosis in mouse models, Zhao *et al*[26] pointed out that these models had differences with HBV-induced immune-mediated liver fibrosis. Using HBV-transgenic mice, the authors observed that blockade of IL-22 reduced Th17 cell recruitment and ameliorated liver inflammation and fibrosis *in vivo*[26]. In another HBV-transgenic mouse model, Zhang *et al*[23] found that the severity of liver injury was reduced by neutralization of IL-22 when splenocytes were transferred from HBV-immunized mice. The authors indicated that this effect was not dependent on HBV inhibition, but instead due to decreased recruitment of all leukocyte subsets into the liver and reduced intrahepatic chemokine expression[23]. The contrasting effects exhibited by IL-22 in different etiology-induced immunity need to be clarified in future studies and maybe 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 CCl_4-treated mice, deletion of the IL-10 gene resulted in significantly more severe fibrosis[82]. In addition, in thioacetamide-treated IL-10 knockout mice, exogenous administration of IL-10 gene reversed an established hepatic fibrosis[83]. Taken together, IL-10 might have potential for future treatment of HBV infection and liver fibrosis. However, since IL-10 exhibits broad biological effects, future studies should also focus on decreasing the side effects.

IL-35: IL-35 is a novel immunosuppressive cytokine produced by Treg and Breg cells, and is being studied for 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 showed that in dominant-negative TGF-β receptor type Ⅱ mice, deletion of the gene encoding the IL-12p35 subunit, which deletes IL-12 and IL-35, induced a Th17 cell response, inhibited a Th1 cell response, and caused liver fibrosis[85]. This results suggests that IL-35 might be closely associated with liver fibrosis.

IL-33: IL-33 belongs to the IL-1 family, and is associated with liver injury and fibrosis in chronic hepatitis[86,87]. In the liver, IL-33 is made by sinusoidal endothelial cells and activated HSCs[87]. Through soluble receptor ST2, IL-33 promotes Th2 cell responses 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 concanavalin A-induced liver injury, administration of IL-33 attenuated hepatitis, whereas deletion of ST2 caused significantly more severe hepatitis[89,90]. Zhao *et al*[91] found that IL-33 might activate Tfh cells, which facilitate humoral immunity against HBV. The specific roles of IL-33 need to be further investigated, in particular the influence of IL-33 on different CD4$^+$ T subsets.

Surface molecules on CD4$^+$ T cells

CD4$^+$ T cells express surface co-inhibitory molecules, including PD-1, cytotoxic T lymphocyte-associated antigen4 (CTLA-4), T-cell immunoglobulin domain and mucin domain-containing molecule 3 (TIM-3), lymphocyte activation gene 3, and CD244. Upregulation of these molecules can result in HBV-specific T cell exhaustion, which is a crucial mechanism in the deviation of homeostasis of adaptive immunity and the consequent persistence and progression of HBV infection[92,93]. These co-inhibitory molecules interact with their ligands expressed on antigen-presenting cells, then deliver signals which decrease cell proliferation and cytokine production[93]. Studies on these co-inhibitory molecules in HBV infection have focused mainly on exhausted CD8$^+$ T cells, but recently more attention has been paid to CD4$^+$ T cells in consideration of their pivotal roles in cell immunity[94]. Furthermore, the expression of these co-inhibitory molecules on CD4$^+$ T cells was shown to be important in other chronic viral diseases 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 and PD-L2[96]. Several studies found that high

levels of PD-1 on CD4$^+$ T cells are strongly linked to exhaustion of HBV-specific CD4$^+$ T cells[93,97,98]. Using a DRB1*01-restricted major histocompatibility complex (MHC) class Ⅱ tetramer, Raziorrouh *et al*[98] found that CD4$^+$ T cells had elevated PD-1 expression; moreover, PD-L1/PD-L2 neutralization reactivated cell proliferation and partially increased production of IFN-γ, IL-2 and TNF-α[98]. Notably, the four patients who responded to the PD-L1/PD-L2 blockade achieved long-term HBV suppression, while the other nine patients who failed to revive T-cell proliferation continued to have high viral loads[98]. Blockade of PD-L1/PD-L2 increased the frequencies of HCV-specific CD4$^+$ T cells and induced cell expansion and production of IFN-γ and TNF-α *in vitro*, whereas influenza- and Epstein-Barr virus-specific CD4$^+$ T cells did not respond significantly to the blockade[95]. The responses of CD4$^+$ T cells to the blockade of PD-L1/PD-L2 may differ from different chronic virus infection. There is limited data on the relationship between PD-1 expression and progression of chronic HBV infection. Xu *et al*[97] reported that although PD-1 expression was upregulated in LC and HCC, the magnitude was small and there was no correlation between PD-1 levels and the severity of liver injury. The role of PD-1 in chronic HBV infection and related liver fibrosis needs further investigation.

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 axis is also essential for the homeostasis of Treg cells[100,101]. Recent studies have indicated that expression of *Tim-3* on CD4$^+$ T cells is upregulated in patients with CHB compared to healthy controls, and TIM-3 levels are positively associated with the extent of HBV infection[93,102]. In addition, the levels of *Tim-3* are decreased after antiviral treatment[102]. However, Raziorrouh *et al*[98] observed a persistent low level of TIM-3 in CHB patients, and TIM-3 blockade had little influence on CD4$^+$ T-cell function. The difference between these studies might be due to the relative paucity of CD4$^+$ T cells and the DRB1*01-restricted MHC class Ⅱ tetramer, as DRB1*01$^+$CD4$^+$ T cells are specific only to HBV core epitope 61-80. In a recent study of mice with chronic lymphocytic choriomeningitis virus infection, treatment with vinegar-processed floss of *Daphne genkwa*, a traditional folk medicine extract, restored function of exhausted virus-specific CD4$^+$ and CD8$^+$ T cells[103]. This restoration might have occurred *via* down-regulation of PD-1 and Tim-3. Moreover, it has been reported that targeting both PD-1 and Tim-3 is an effective strategy to restore exhausted CD8$^+$ T cells during chronic viral infection[104]. Future studies should focus on the blockade of both TIM-3 and PD-1 on HBV-specific CD4$^+$ T cells.

CTLA-4: CTLA-4 is expressed on activated and regulatory CD4$^+$ T cells to prevent over-activation and maintain tolerance[105]. It is widely reported that CTLA-4 has a close correlation with HBV infection in promoting Th2 cell responses[106-108]. Several groups found that CTLA-4 gene polymorphisms might be associated with HBV progression and viral persistence[107,109]. However, expression of CTLA-4 on virus-specific CD4$^+$ T cells in chronic HBV infection is still controversial. Recent years have witnessed prominent effects of CTLA-4 blocking. Blockade of CTLA-4 by the monoclonal antibody tremelimumab has been tested in patients with HCC and HCV-induced LC, and shown substantial antitumor and antiviral effects[110]. In *Propionibacterium acnes* and lipopolysaccharide-induced mouse models of fulminant hepatitis, all mice injected with adenovirus encoding a CTLA-4 immunoglobulin construct survived, whereas most of the control mice died, suggesting that the construct could be useful for treatment of severe liver injury[111]. Together, these studies have shown the importance of CTLA-4 in chronic viral infection and associated disease progression. Future studies should investigate the correlation of CTLA-4 with the homeostasis of HBV-specific CD4$^+$ T cells.

Cannabinoid receptor 2: In addition to co-inhibitory molecules on the surface of CD4$^+$ T cells, surface receptors such as cannabinoid receptor 2 (CB2) have received attention because of their anti-inflammatory and anti-fibrotic properties in mouse liver[112]. CB2 is abundantly expressed on almost all immune cells[113]. In CB2-deficient mice with bile duct ligation, intrahepatic Th17 cells and IL-17 levels were increased compared with wild-type mice, whereas the CB2 agonist JWH-133 reduced the differentiation and function of Th17 cells *in vitro*[112]. In CB2-deficient mice treated with CCl_4, increased ALT levels and hepatocyte apoptosis, and delayed liver regeneration were shown, while JWH-133 displayed hepatoprotective property in CCl_4 treated wild types[114]. Thus, activating CB2 on Th17 cells may be effective for treatment of liver fibrosis. It will 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. The disequilibrium of CD4$^+$ T cells contributes to the disease, and restoring homeostasis may help greatly to reestablish effective immunity against HBV-related pathological processes. However, there are still many problems to be resolved. First, the specific regulatory mechanisms of CD4$^+$ T-cell homeostasis, especially the balance between 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 always worthy of further

research.

There is still a long way to go in the restoration of homeostasis of CD4$^+$ T cells in HBVLF, but future studies 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 CD4$^+$ T cells, as well as their interactions with other cells, especially their links with innate immunity. For instance, we previously found that the fibrotic factor high-mobility group box1 (HMGB1), a damage-associated molecular pattern molecule, could transmit signals from necrotic cells to innate immune cells and then to CD4$^+$ T cells in CHB patients through the axis of HMGB1-TLR4-IL-6-Treg/Th17 balance[115]. As a result, HMGB1 promotes Th17 cell responses and inhibits Treg cell responses, thus exerting pro-inflammatory and pro-fibrotic effects[115]. Therefore, future studies on the homeostasis of CD4$^+$ T cells should include their links with innate immunity.

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