Hepatol Int (2014) 8:7–9
DOI 10.1007/s12072-013-9506-4

EDITORIAL

# Balance lost: T cell immunity in progressive HBV infection

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Received: 12 October 2013 / Accepted: 29 November 2013 / Published online: 9 January 2014


An efficient, coordinated immune response is key to the resolution of viral infections. Indeed, the spontaneous elimination of hepatitis B virus (HBV) during acute infection is associated with the emergence of functionally competent antiviral CD8+ and CD4+ T cell responses [1]. In contrast, chronic infection is characterized by the presence of dysfunctional HBV-specific CD8+ T cells that are unable to control viral infection [2, 3]. Since current antiviral therapies are able to cure only a small number of patients, the restoration of antiviral HBV-specific CD8+ T cells is a promising goal for novel therapeutic strategies. It is likely that several factors contribute to CD8+ T cell dysfunction in chronic HBV infection, including the action of regulatory T cells (Tregs), depletion of arginine in the inflamed liver microenvironment causing reduced T cell receptor signalling, release of immunoregulatory cytokines, enhanced T cell apoptosis, exposure to high loads of viral antigen, and the tolerogenic liver environment [2–4]. Moreover, several reports have described the up-regulation of inhibitory receptor expression by HBV-specific CD8+ T cells [5–12]. These studies suggest that HBV-specific CD8+ T cells are in a state of T cell exhaustion. Exhausted T cells are characterized by poor effector functions, expression of inhibitory receptors, and a distinct "exhaustive" differentiation and transcriptional state [13]. In addition to HBV-specific CD8+ T cells, CD4+ T cells play an important role in chronic HBV infection. Indeed, several reports have reported an up-regulation of Tregs in chronic HBV infection [14–17] that were able to impair HBV-specific CD8+ T cell function. Tregs play a crucial role in the immune system by preventing excessive inflammatory T cell responses and limiting immunopathology. However, the regulatory function of regulatory T cells may be counteracted by proinflammatory T cell responses. In particular, IL-17-producing CD4+ T cells (TH17 cells) are critically involved in the induction and maintenance of inflammation and are enriched in inflammatory diseases. TH17 cells are able to secrete several potentially proinflammatory cytokines depending on STAT3 signaling, including IL-17, IL-22, GM-CSF, and TNF that modulate the tissue response during inflammation [18, 19]. Of note, the frequency of TH17 cells increases with disease progression in chronic HBV infection. Indeed, an enrichment of circulating and intrahepatic TH17 cells is observed in liver inflammation and correlates with elevated liver enzymes and histological activity index [20]. Thus, a picture emerges in which Tregs may contribute to immune tolerance in chronic HBV infection by limiting HBV-specific CD8+ T cell function resulting in T cell exhaustion, but this effect may be overcome by TH17 cells, causing immunopathology. The mechanisms that are responsible for maintaining the balance of Tregs and TH17 cells are currently unclear. However, it seems reasonable to speculate that a dysregulated cellular immune balance is responsible for the different immunological stages of chronic HBV infection (e.g., immune tolerance phase with high viral replication in the absence of liver damage, and immune activation phase with significant liver inflammation and reduced viral replication and phases of relative immune control with low viral replication and low liver inflammation). Moreover, it is thought that the dysregulation of the antiviral response with a shift to proinflammatory T cell responses may lead to chronic hepatic inflammation resulting in progressive liver disease, liver cirrhosis, and hepatocellular carcinoma (Fig. 1).

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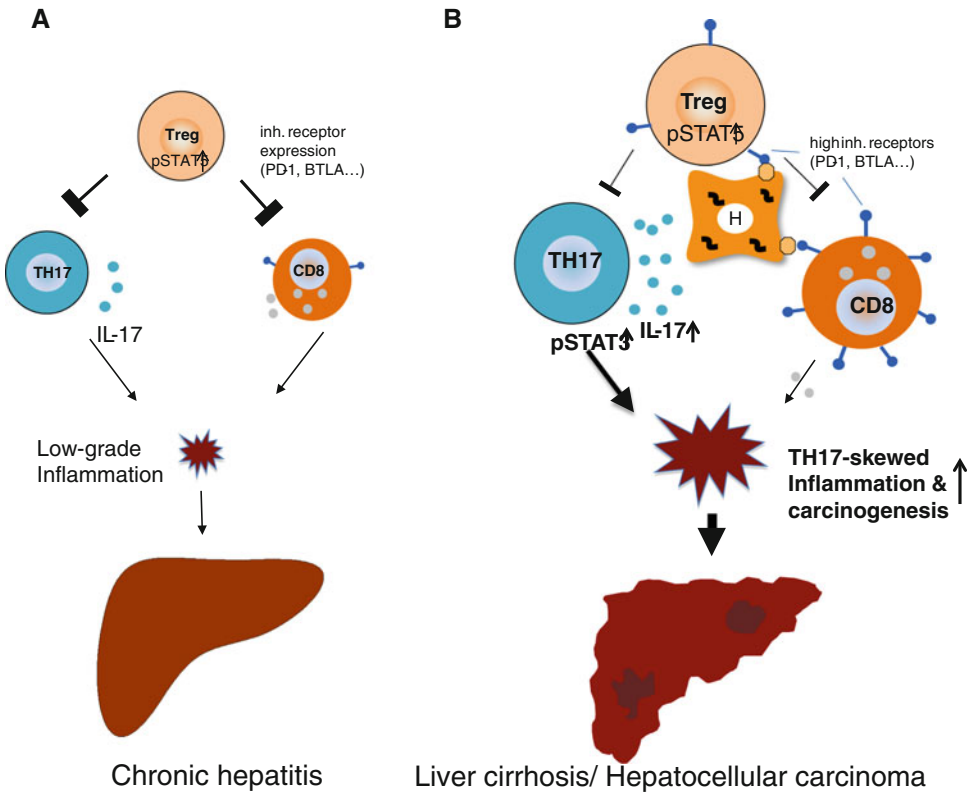


**Fig. 1** **a** In chronic hepatitis, regulatory T cells are thought to sufficiently control proinflammatory TH17 and CD8+ T cell activity, resulting in lowgrade inflammation. **b** Progression to liver cirrhosis and hepatocellular carcinoma is characterized by increased TH17 cells frequency, STAT3 phosphorylation and increased inhibitory receptor expression on CD8+ T cells and, possibly, on regulatory T cells, resulting in negative costimulation upon ligand binding. The net immmune balance is shifted to TH17-skewed proinflammatory and procarcinogenic pathways.

In the study published in this issue of *Hepatology International*, Chen et al. [21] analyzed important regulatory pathways of T cells in patients with different stages of chronic HBV infection, including liver cirrhosis and hepatocellular carcinoma (HCC). In particular, they addressed the balance of proinflammatory T helper cells by analyzing the frequency of TH17 cells and Tregs, STAT phosphorylation, and the balance between co-stimulatory and co-inhibitory signaling.

By analyzing the frequency of TH17 cells, the authors observed an up-regulation of TH17 cells in HBV patients with liver cirrhosis and with HCC, in association with an increased phosphorylation of the transcriptional activator STAT3 important for TH17 differentiation. In patients with liver cirrhosis, the authors also observed an increase in Tregs, suggesting a concomitant up-regulation of TH17 and Tregs in liver cirrhosis, but not in HCC.

Since the frequencies of TH17 cells and Tregs were comparable between healthy controls and patients with chronic HBV in the absence of liver cirrhosis and HCC, these results suggest that global changes of TH17 cells and Tregs occur late in HBV infection and may characterize phases of progressive disease. Indeed, a recent study by Zhang et al. [16] observed a similar up-regulation of TH17 and Tregs in patients with progressive acute-on-chronic liver failure. Thus, the up-regulation of TH17 cells and Tregs in progressive HBV infection is associated with enhanced liver inflammation indicating impaired Treg function.

The activation of T cells is positively regulated by co-stimulatory signals (e.g., mediated by CD28), while negative regulation is mediated by co-inhibitory signaling (e.g., via PD-1 or BTLA). Next to the upregulation of inhibitory receptor expression observed by exhausted CD8+ T cells, inhibitory pathways may be responsible for the regulation of Treg function. Indeed, in HCV infection, inhibitory signaling by the PD-1/PD-L1 pathway impaired regulatory T cell function and limited STAT5 phosphorylation. Blockade of PD-L1 signaling on Tregs resulted in the functional restoration of Tregs [22], suggesting that up-regulation of inhibitory receptors by Tregs may effectively contribute to inflammation by limiting regulatory T cell function. In the study performed by Chen et al., the authors analyzed the expression of several co-stimulatory (CD28, ICOS, LIGHT) and co-inhibitory (PD-1, CD160, BTLA) molecules by T cells from patients with different stages of HBV infection. Interestingly, they observed an up-regulation of inhibitory receptors in patients with liver cirrhosis and HCC, while the expression of co-stimulatory molecules was not altered compared to healthy controls. However, it remains to be determined whether inhibitory receptor expression was up-regulated on exhausted CD8+ T cells or Tregs.

In sum, in agreement with previous studies, the authors observed a significant alteration of the frequency of TH17 cells and Tregs and an up-regulation of inhibitory receptors in patients with liver cirrhosis and HCC due to chronic

HBV infection. These findings raise the question why the up-regulation of regulatory T cells and co-inhibitory pathways is unable to control inflammation and disease progression. Further mechanistical and longitudinal studies will be required to dissect the exact role of TH17 cells, Tregs, and inhibitory receptor expression in HBV progression. This study highlights the dramatic changes of the adaptive immune system that occur during the progression of chronic HBV infection.

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