Research progress in host immune response during hepatitis B virus infection

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Hepatitis B virus (HBV) infection is a global health problem that can cause serious life-threatening liver diseases such as cirrhosis and hepatocellular carcinoma.[1] Under most circumstances, HBV is a non-cytopathic virus (does not directly kill hepatocytes); thus, the liver inflammation and fibrosis have been shown to be predominately mediated by the infiltration of immune cells.[2] Even through long term anti-viral therapy, patients can rarely achieve functional cure. However, spontaneous resolution of acute and chronic hepatitis B (CHB) has indicated the possibility of immune control of the HBV infection. Patients with CHB have been shown to have defects in immune response, which results in persistent viral replication and liver inflammation.

Most viruses can be detected by immune cells through pathogen recognition receptors (PRRs) early after infection. During the activation of the innate immune system, PRRs recognize HBV and affect viral replication. HBV was once considered as a "stealth virus" that does not induce innate immune response; however, several lines of evidence have challenged this view. Intrahepatic gene expression profiling showed a strong impairment of innate immune responses in patients with CHB as compared to non-infected controls. The innate immune response pathways including interferon (IFN) stimulated genes, Toll-like and PRR pathways were strongly down-regulated, but not directly correlated with HBV replication.[3]

The intrinsic antigen-presenting cells (APCs) in the liver can either induce immune tolerance (IT) to help viruses escape immune clearance or mediate effective anti-viral immune response against HBV infection. Liver sinusoidal endothelial cells (LSECs) are unique liver resident APCs; CD4+ and CD8+ T cell tolerance induced by LESCs may be disrupted by different regulatory mechanisms. Stimulating the nucleotide binding oligomerization domain containing 1 pathway could induce the function maturation of LSECs and dendritic cells, subsequently enhancing T-cell responses and inhibiting HBV replication.[4] Matrix metalloproteases 2/9-mediated soluble CD100 release could activate LSECs, thereby enhancing HBV-specific CD8+ T-cell response and accelerating HBV clearance.[5] Kupffer cells (KCs) are liver resident macrophages, which can be divided into pro-inflammatory (M1) and immunoregulatory (M2) phenotypes. KCs from HBV-infected patients were shown to express higher levels of anti-inflammatory markers and secret more interleukin (IL)-10 when compared to those from non-infected patients, and exposure of primary human liver macrophages to HBV led to reduced secretion of pro-inflammatory cytokines like IL-6 and IL-1β.[6] Plasmacytoid dendritic cells (pDC) and cytokines play an important role in occurrence and recovery of HBV infection. The enhanced function of pDC might involve triggering the immune response from IT phase to hepatitis active phase.[7] IFN-α, an important cytokine with immune stimulation action, is mainly secreted by pDC, were elevated significantly in CHB patients when compared to patients in IT phase.[8]

Adaptive immune responses play a vital role in clearing HBV from infected hepatocytes. Therefore, restoring and enhancing the quantity and function of HBV-specific T cells and B cells would be critical for achieving a functional cure. A recent study detected HBV-specific CD8+ T cells by applying a peptide-loaded major histocompatibility complex I tetramer-based enrichment strategy and found that HBV-specific CD8+ T cells targeting core and polymerase epitopes are not terminally exhausted but exhibit a memory-like phenotype in CHB patients with low viral load, and further confirmed that these T cells differed in frequency, phenotype, and function.[9] Another study also found low-frequency core and polymerase-specific CD8+ T cells in chronic infection and revealed that HBV-specific

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001096

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Chinese Medical Journal 2020;133(22)

Received: 20-04-2020 **Edited by:** Qiang Shi

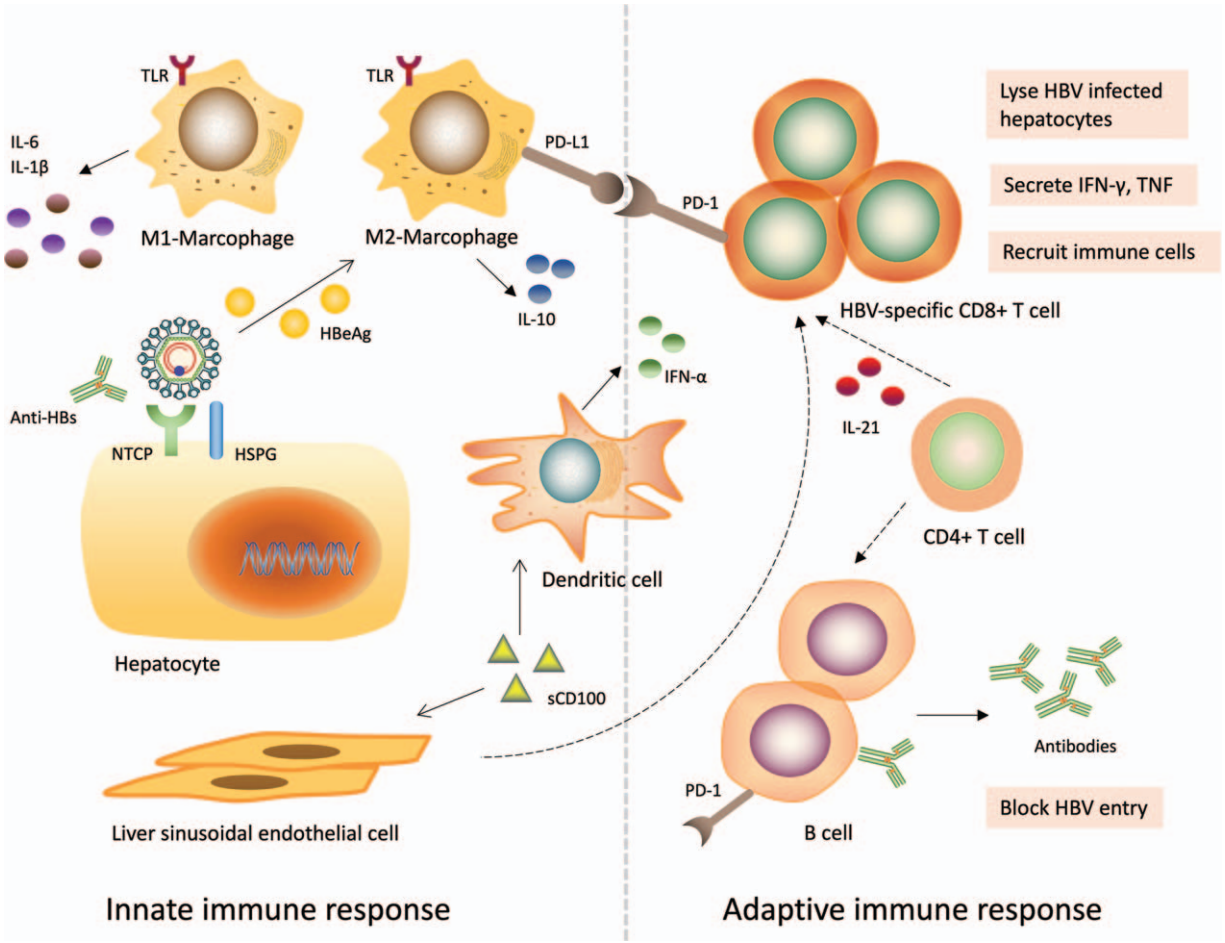

Figure 1: The important research hotspots concerning the immunopathogenesis of the persistence of HBV infection. HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HSPG: Heparan sulfate proteoglycan; IL: Interleukin; IFN: interferon; NTCP: Sodium taurocholate cotransporting polypeptide; PD-1: programmed death 1; PD-L1: programmed death ligand-1; sCD100: soluble CD100; TLR: Toll-like receptor.

T cell differentiation, function, and regulation not only differed by the targeting epitopes, but also by the stages and outcomes of HBV infection.[10] T-cell responses during discontinuation of nucleos(t)ide analog (NA) therapy is still unclear. Relapse of active HBV replication after discontinuation of therapy might altered the phenotype of T cells and enhanced its responsiveness *in vitro*. T cells from patients with subsequent hepatitis B surface antigen (HBsAg) loss showed a less exhausted phenotype that expressed low levels of programmed death 1 (PD-1), and blocking of programmed death ligand-1 further enhanced HBV-specific CD4+ and CD8+ T cell responses after NA cessation.[11] Functional recovery of exhausted HBV-specific T cells are important for viral control. IL-21 secreted by activated CD4+ T cell could promote the proliferative capacity and enhance the anti-viral effect of HBV-specific CD8+ T cells, additionally down-regulated expression of PD-1, which may provide critical support to viral clearance in chronic HBV infection.[12]

Over the past few decades, studies on HBV-specific B-cell responses have been largely neglected. Recently, a dual fluorochrome-conjugated method was developed for the detection of HBV-specific B cells, and results showed that hepatitis B core antigen-specific B cells presented a higher frequency when compared to HBsAg-specific B cells, and matured efficiently in patients with CHB.[13] HBsAg-specific B cells from patients with CHB were demonstrated to be defective in antibody production, consistent with undetectable anti-HBs antibodies *in vivo*, and had an accumulation of atypical memory B cells with high expression of PD-1.[14] Dysfunctional virus-specific B cells could be partially recovered by PD-1 blockade, and the presence of IL-2 and IL-21 in CD40L-expressing feeder cells partially restored HBsAg-specific B cell maturation.[15]

The impact of HBV infection on the intrahepatic immune microenvironment remains a hotspot for the research and development of new drugs that could regulate anti-viral immune response against HBV, there were many research progress which can help us better understand the role of the innate and adaptive immunity [Figure 1]. Overall, a better understanding of different aspects of HBV immunopathogenesis could enable us to design targeted immunotherapy strategies that might achieve long-lasting control of HBV, even functional cure.

Conflicts of interest

None.

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How to cite this article: Yu XQ, Zhang XX. Research progress in host immune response during hepatitis B virus infection. Chin Med J 2020;133:2746–2748. doi: 10.1097/CM9.0000000000001096