Journal of Clinical and Translational Hepatology **2021** vol. 9(4) | 592–597
DOI: 10.14218/JCTH.2021.00051

Review Article

B Cell-mediated Humoral Immunity in Chronic Hepatitis B Infection

Yang Li[1#], Shengxia Yin[2#], Rahma Issa[3], Xin Tong[2], Guiyang Wang[2], Juan Xia[2], Rui Huang[2], Guangmei Chen[4], Dan Weng[1], Chen Chen[5], Chao Wu[2*] and Yuxin Chen[6*]

[1]School of Environmental and Biological Engineering, Nanjing University of Science & Technology, Nanjing, Jiangsu, China; [2]Department of Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China; [3]Department of Infectious Diseases, Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University, Nanjing, Jiangsu, China; [4]Department of Infectious Diseases, Jiangsu Province Hospital of Chinese Medicine, Nanjing, Jiangsu, China; [5]Department of Clinical Pharmacology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China; [6]Department of Laboratory Medicine, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China

Received: 3 February 2021 | **Revised:** 24 April 2021 | **Accepted:** 6 May 2021 | **Published:** 27 May 2021

Abstract

B cell-mediated humoral immunity plays a vital role in viral infections, including chronic hepatitis B virus (HBV) infection, which remains a critical global public health issue. Despite hepatitis B surface antigen-specific antibodies are essential to eliminate viral infections, the reduced immune functional capacity of B cells was identified, which was also correlated with chronic hepatitis B (CHB) progression. In addition to B cells, T follicular helper (Tfh) cells, which assist B cells to produce antibodies, might also be involved in the process of anti-HBV-specific antibody production. Here, we provide a comprehensive review of the role of various subsets of B cells and Tfh cells during CHB progression and discuss current novel treatment strategies aimed at restoring humoral immunity. Understanding the mechanism of dysregulated B cells and Tfh cells will facilitate the ultimate functional cure of CHB patients.

Citation of this article: Li Y, Yin S, Issa R, Tong X, Wang G, Xia J, *et al*. B cell-mediated humoral immunity in chronic hepatitis B infection. J Clin Transl Hepatol 2021;9(4):592–597. doi: 10.14218/JCTH.2021.00051.

Introduction

Hepatitis B virus (HBV) infection remains a significant cause of liver cirrhosis and hepatocellular carcinoma globally, especially in developing countries like China. In 2015, the World Health Organization (WHO) estimated that 257 million individuals live with chronic hepatitis B (CHB) worldwide,[1,2] resulting in 887,000 yearly deaths, mostly due to HBV infection-related hepatocellular carcinoma and cirrhosis.[3–5]

The challenge to CHB treatment is the failure to clear covalently closed circular DNA (referred to as cccDNA), which can give the virus the capacity to evade the host immune system, making a complete sterilizing cure unlikely to be feasible.[6] On the other hand, a functional cure is defined as a sustained clearance of hepatitis B surface antigen (HBsAg) with or without seroconversion to anti-HBs antibodies after a finite course of therapy, but with the persistence of residual cccDNA. The functional cure of CHB has been considered as a feasible clinical treatment goal,[7,8] which is correlated with improved clinical outcomes.[9] Nevertheless, only a small proportion of patients reach this milestone.[10,11]

The complex interaction between HBV and the host immune system drives the process of chronic HBV infection, in which the anti-HBV adaptive immune system processes facilitate the clearance of HBV. Despite T cell responses having been well-studied in HBV infection, the beneficial biological function of B cells for functional cure of CHB has been consistently neglected. In addition, T follicular helper (Tfh) cells which regulate the B cell-mediated humoral immune responses have been identified as phenotypically distinct, leading to humoral immunity defection in patients with CHB.[12] Hence, in this review, we will discuss the role of B cell-mediated humoral responses during chronic HBV infection and the current promising treatment strategies to induce robust anti-HBV humoral responses (Fig. 1).

Protective role of antibody in HBV control and clearance

B cell-mediated humoral immune responses are essential for HBV control and clearance. Universal vaccination against HBV has remarkably decreased HBV infection rate, since anti-HBsAg antibodies (i.e. anti-HBs) induced by immunization could prevent HBV infection.[13] It is considered that those individuals with an anti-HBs concentration of ≥10 mIU/mL were immune against HBV infection, while those with an anti-HBs concentration of <10 mIU/mL might re-

Keywords: Chronic hepatitis B (CHB); B cell; T follicular helper (Tfh) cells; Antibody; Therapeutics.

Abbreviations: HBV, hepatitis B virus; CHB, Chronic hepatitis B; Tfh, T follicular helper; HBsAg, hepatitis B surface antigen; APCs, professional antigen-presenting cells; IA, immune active; IT, immune tolerance; TLR, Toll-like receptor; PD-1, programmed cell death receptor-1; atMBCs, atypical memory B cells; Bregs, regulatory B cells; Tregs, regulatory T-cells; IL-10, interleukin -10; GCs, germinal centers; CXCR, chemokine receptor.

[#]Contributed equally to this work.

[*]**Correspondence to:** Yuxin Chen, Department of Laboratory Medicine, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu 210008, China. ORCID: https://orcid.org/0000-0001-5955-687X. Tel: +86-25-8968-3827, Fax: +86-25-8330-7115, E-mail: yuxin_chen2015@163.com; Wu Chao, Department of Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu 210008, China. ORCID: https://orcid.org/0000-0002-1657-010X. Tel: +86-25-8310-5890, Fax: +86-25-8330-7115, E-mail: dr.wu@nju.edu.cn

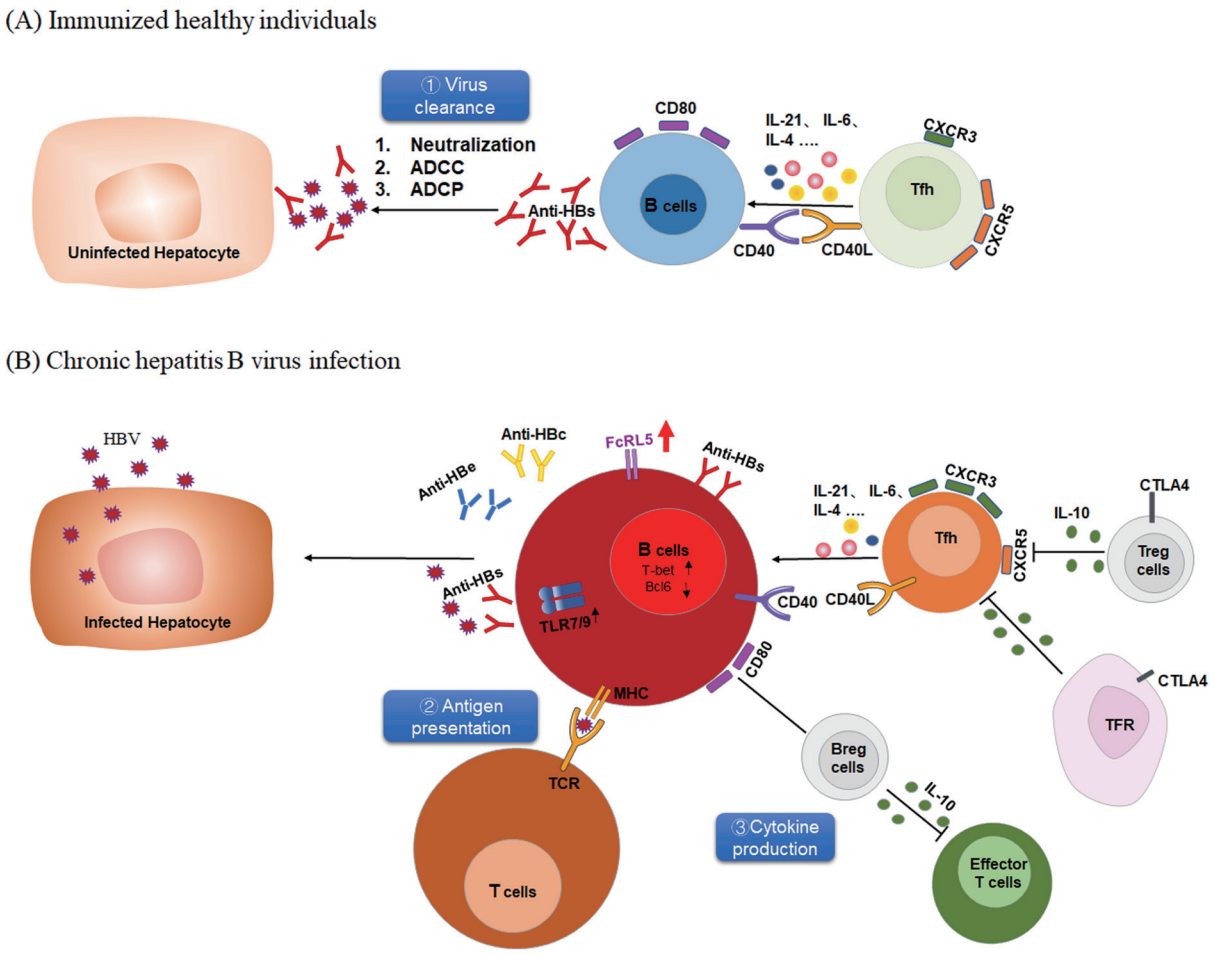

Fig. 1. B cell-mediated humoral immunity in immunized healthy individuals and CHB patients. (A) HBsAb production by HBsAg-specific B cells in immunized healthy individuals plays a pivotal role in the clearance of HBV. A major antiviral role for HBsAb is viral clearance, mediated by neutralization, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. Tfh cells could assist B cell function by expressing cytokines such as IL-21, IL-6 and IL-4 and direct interactions through CD40L/CD40. (B) In CHB patients, B cells were phenotypically dysfunctional with increased expression of T-bet, TLR7/9 and FcRL5. During CHB infection, despite HBcAg-specific B cells being class-switched memory B cells and secrete anti-HBc, HBsAg-specific B cells fail to mature efficiently into antibody secreting cells, leading to the scarcity of serological anti-HBs. Beyond the traditional role of antibody production, HBV-specific B cells might efficiently serve as a primary source of APC for T cells and induce CTLs responses. Moreover, B cells can produce cytokines such as IL-10 to inhibit the function of effector T cells and enhance Treg cell function. TFR and Treg cells can impair the Tfh function by secreting IL-10 and expressing CTLA4. The dysregulated B cells, Tfh cells, TFR cells and Treg cells might contribute to the defective function of B cell mediated humoral immunity during CHB infection. HBV, hepatitis B virus; CHB, chronic hepatitis B; Tfh, T follicular helper; HBsAg, hepatitis B surface antigen; APCs, antigen-presenting cells; TLR, toll-like receptor; IL-10, interleukin-10.

quire an additional booster vaccine dose.[14–16]

The specific antibodies against different HBV protein components are one of the major approaches for B cells to be involved in anti-HBV infection, such as antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B e antigen (anti-HBe) and anti-HBs. Anti-HBc and anti-HBe serve as diagnostic biomarkers for HBV infection, while anti-HBs antibody is the only antibody that can specifically recognize and bind to HBsAg,[17,18] thus serving an important role in HBsAg clearance.[19] First, anti-HBs can not only block HBV entry by binding to free HBV viral particles as protective neutralizing antibodies to reduce viral load *in vivo*[20–22] but it also can mediate antigen-dependent cellular cytotoxicity and antigen-dependent cellular phagocytosis to clear infected cells.[23] HBV reactivation and hepatitis are well recognized complications that occur in patients who have undergone cytotoxic chemotherapy or immunosuppressive therapy.[24] For example, high incidence of HBV reactivation was observed in lymphoma patients who were HBs-negative/anti-HBc-positive with or without anti-HBs and receiving rituximab-containing chemotherapy.[25] Negative anti-HBs at baseline is an independent risk factor for HBV reactivation in patients with resolved CHB, compared with higher titer of anti-HBs ≥100 mIU/mL.[26] Moreover, adoptive transfer of HBV-specific immunity with the liver from an immune living liver donor leads to successful transfer of HBV-specific humoral and cellular immunity, which might be responsible for the delay of reinfection and a reduction of viral load.[27] Therefore, anti-HBs is essential to alleviate disease advancement and prevent reinfection during CHB.

Several neutralizing monoclonal antibodies (referred to as mAbs) specific to HBsAg have been reported. For example, human mAbs including 2H5-A14[28] and Bc1.187[29] that block the engagement of HBsAg to sodium taurocholate co-transporting polypeptide potently neutralize HBV *in vitro*. In addition, they could decrease viremia *in vivo* in an HBV mouse model. E6F6 that recognizes an evolutionarily conserved epitope (GPCK(R)TCT) not only prevented initial HBV infection and reduced the viral dissemination in human-liver-chimeric mice but also facilitated the restora-

tion of anti-HBV T cell response in hydrodynamic injection-based HBV carrier mice.[30] Furthermore, *in vivo* delivery of a DNA-encoded monoclonal antibody plasmid can efficiently neutralize HBV virus *in vitro.*[31] These antibodies can serve as a promising immunotherapeutic regimen or immunoprophylaxis for HBV infection.

Beyond the traditional role of antibody production, B cells also may play a vital role as professional antigen-presenting cells (APCs) during CHB infection.[25,32] Compared to the classical non-B cell APCs, HBcAg-specific B cells might efficiently serve as a primary source of APCs for native HBcAg-specific T cells.[33–36] In addition, B cells can induce an HBcAg-specific cytotoxic T lymphocytes (CTLs) response and further prevent immune tolerance by the cross-presentation of HBcAg on major histocompatibility complex-I (i.e. MHC-I) to specific $CD8^+$ T cells. At the same time, HBsAg is a special exogenous antigen, which can be involved to MHC-I molecules expressed on B cells.[37,38]

Immune dysfunction of B cells during CHB infection

HBV infection has exerted a significant impact on the global B cell compartment and HBV-specific antibody secretion.[39,40] Global peripheral B cells were activated with reduced functional capacity, while anti-HBs-secreting B cells were rarely detected.[19,41] Additionally, although total immunoglobulin G (IgG) in the serum among CHB patients is remarkably greater than in that of healthy controls, the absence of HBV-specific antibodies was observed.[39,42,43] B cell hyperactivation, differentiation disorder, activation of inhibitory signal and regulatory B cells may contribute to immune dysfunctions observed in CHB patients.[44,45]

A hallmark of chronic hepatitis infections, such as hepatitis C virus is the presence of immune exhausted virus-specific $CD8^+$T cells, characterized by their inability to secrete antiviral cytokines and an upregulation of inhibitory receptors such as programmed cell death receptor-1 (referred to as PD-1).[46] B cell hyperactivation is characterized by enhanced expression of activation markers with displayed impaired function, especially in patients at immune active (IA) and immune tolerance (IT) stage.[45,47] Overall, the mechanism of the hyperactivation of B cells remains to be clarified. Xu *et al*[19] reported that the B cell hyperactivation could be induced by increased interferon (IFN)-α and sCD40 ligands in IA patients. The increased activation of CD71 and CD69 expressed on B cell accounts for the B cell hyperactivation.[48,49] A high level of Toll-like receptor (TLR) 9 expression likely contributes to the functional hyperactivation of B cells in CHB patients.[50] A recent study revealed that B cells from CHB patients had a markedly reduced capacity to generate CD39/CD73-dependent extracellular adenosine and exhibited increased activation markers after adenosine-production blockade, suggesting CD39/CD73/adenosine pathway might contribute to B cell hyperactivation.[51]

The frequency of HBsAg-specific B cells was comparable in both CHB patients and immunized healthy individuals, while anti-HBs in CHB patients were detected at low level or were even undetectable.[52] In CHB patients, there was a unique population of B cell subsets with high levels of inhibitory receptors, including PD-1, which resemble $CD21^-CD27^-$ atypical memory B cells (referred to as atMBCs). These atMBCs had elevated level of defective signals, which might be responsible for defective capacity of survival, cytokine production and differentiation into antibody-secreting cells. Such atMBCs were found to be expanded in CHB patients and to have accumulated quickly in the HBsAg-specific compartment, which might reduce anti-HBs secretion[47,53] and enhance B cell hyperactivation in CHB patients.[41,54,55] In addition, the transcription factor T-bet was also upregulated in $CD21^-$ B cells during murine and human HBV infections,[56] which may be correlated with the inadequate production of HBsAg-specific B cells among CHB patients.[57–59] Moreover, chemokine receptor 3 (CXCR3), Fc receptor-like 4 (FCRL4) and FCRL5 are upregulated in B cells and associated with B cell immune dysfunction during HBV infection.

A regulatory subset of B cells (regulatory B cells, Bregs) is elevated in CHB patients,[44] which has been reported to inhibit liver inflammation and immune disorders in mouse models.[60,61] Previous studies showed that the frequency of Bregs had a significant correlation with alanine aminotransferase (ALT) and glutamic oxaloacetic transaminase (AST).[62] Furthermore, CHB patients in the IA phase exhibit increased Bregs due to inflammatory responses.[63] However, the underlying mechanism of the Bregs' elevation during CHB infection remains unclear. Bregs could suppress $CD8^+$ T cell responses, which might serve a pathogenic role by secreting interleukin-10 (IL-10), enhancing the function of regulatory T-cells (Tregs),[63] and suppressing T cell from secreting proinflammatory cytokines in various autoimmune diseases.[63,64] During CHB infection, Bregs have a crucial role in suppressing antiviral immune response by producing IL-10.[65] Notably, in HBeAg-negative CHB patients, serum IL-10 level was correlated with high virus load and advanced liver inflammation,[66,67] while blockade of IL-10 could improve vaccine efficacy and disease resolution in CHB patients.[68–70]

A recent study elegantly characterized the phenotype and functional impairment of HBsAg-specific B cells and HBcAg-specific B cells.[71] Of note, B cell response against HBsAg and HBcAg is different during CHB infection. HBcAg-specific B cells are present at higher frequency than HBsAg-specific B cells. Further, HBcAg-specific B cells are class-switched memory B cells and secrete antibodies, while HBsAg-specific B cells failed to mature efficiently into antibody secreting cells. The transcriptomic analysis showed that HBV-specific B cells had an mRNA expression pattern that differs from global memory B cells and express cross-presentation and innate immune genes, suggesting additional roles of HBV-specific B cells beyond the production of antibodies.

Multifunctional roles of Tfh cell subsets in CHB infection

T follicular helper (Tfh) cells are a unique subset of $CD4^+$ T cells, which can directly help B cells secrete antibodies in germinal centers (referred to here as GCs).[72–74] By colocalizing with B cells and expressing costimulatory signals as well as various cytokines, Tfh cells directly interact with B cells, facilitate B cell differentiation into long-lived plasma cells and memory B cells with high affinity, and facilitate the formation of GCs.[75–77]

Peripheral $CD4^+CXCR5^+$ T cells are considered as circulating memory $CD4^+$ Tfh cells. Peripheral circulating memory Tfh cells had similar phenotypic and functional properties as Tfh cells in the GC, known as GC Tfh cells, such as enhanced expression of CXCR5, stimulation of B cell maturation, terminal differentiation of B cells into antibody-producing plasma cells, and isotype switching. By the dominant transcriptional factors and cytokines, the circulating human memory Tfh cells have been divided into three subsets: Tfh1 ($CXCR3^+CCR6^-$); Tfh2 ($CXCR3^-CCR6^-$); and Tfh17 ($CXCR3^-CCR6^+$).[78] It is considered that blood memory Tfh2 and Tfh17 cells can induce naïve B cells to produce IgGs. Interestingly, Tfh2 cells can preferably induce the secretion of IgG and IgE, and Tfh17 cells can effectively promote IgG and especially IgA secretion.[79] while Tfh1 cells enhance protective antibody responses, making the memory B cells differentiate into effector B cells.[79,80]

It has been well established that Tfh cells have an essential role in various infectious diseases, such as *Plasmodium vivax* infection,[81] acute malaria,[82] CHB,[72] human immunodeficiency virus,[83] and tuberculosis.[84] Indeed, Tfh cells also play a vital role during CHB progression. The frequency of circulating Tfh cells ($CXCR5^+CD4^+$ T cells, cTfh cells) was correlated with the serum levels of ALT and AST,[85] suggesting that cTfh cells may be involved in HBV-specific immune responses. Further evidence showed that CHB patients have a significant increase of Tfh cells compared to healthy controls.[12] The frequency of $CD4^+CXCR5^+$ T cells in IA patients was higher than that of IT patients and healthy individuals,[86,87] suggesting high frequency of $CD4^+CXCR5^+$ Tfh cells could be a biomarker to assess the immune status of CHB patients. cTfh cells secrete IL-21 to facilitate HBeAg seroconversion.[88] On the other hand, HBsAg is a T cell-dependent antigen, and seroconversion of HBsAg also requires the assistance of Tfh cells. A unique group of $CXCR5^+CD8^+$ T cells with minimal levels of inhibitory receptors exerted its potent cytotoxicity to control viral replication by migrating into B cells follicles during CHB.[51,89,90] A subset of $CD25^+FOXP3^+$ Treg-like cells in cTfh cells that was enriched in patients, known as follicular regulatory T (referred to as TFR) cells, could suppress helper function of Tfh cells.[91] In a mouse model with persistent HBV infection, the function of HBsAg-specific cTfh cells was blocked by Treg cells, whereas the depletion of Treg cells could restore the cTfh function.[92] Moreover, a group of type 1 regulatory T (i.e. Tr1)-like cells migrate from the liver to the draining lymph node and can inhibit peripheral anti-HBV immunity by negatively regulating GC B cells and Tfh cells.[93]

Novel CHB treatment strategies targeting B cells

The widely used clinical standard first-line antiviral therapeutics for chronic HBV infection include IFNs and nucleoside analogs (commonly known as NAs). IFNs have a strong antiviral effect and immune-mediated function, which promotes antiviral innate and adaptive immunity. Based on the genetic, structural and functional characteristics and their receptors on the cell surface, the IFN family is classified into three major types: type-I; type-II; and type-III. Type-I IFNs (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) has been approved for the treatment of CHB infection.[94] Pegylated-IFN-α eliminates the production of HBsAg and is well tolerated in HBeAg-negative CHB patients.[95–98] In addition to the previously reported efficiency of pegylated-IFN on T cells and natural killer cells,[99] B cells may also play an essential role in this process.[100–102] Pegylated-IFN-α treatment might exert the immunomodulatory effect by remodeling B cell compartments, which was correlated with a sustained increase in sCD30 levels and decrease of plasma HBsAg.[103,104]

TLR agonists and checkpoint inhibitors are an emerging treatment strategy for CHB patients. TLR7 is highly expressed on B cells and has been proven to inhibit antibody production. As an oral agonist of TLR7, GS9620 is currently in clinical assessment to treat CHB patients.[105] Preclinical study showed that GS9620 treatment significantly induced an intrahepatic transcriptional profile enriched with $CD8^+$ T cells and B cells, contributing to clearance of HBV in a chimpanzee model.[106] Also, TLR9 agonists such as CPG 7909 or 1018 ISS co-administrated with HBsAg induced robust antibody responses among CHB patients.[107] Therefore, combined immunotherapeutic agents might be necessary to restore B cell function and induce the desired B cell antibody response.

HBV therapeutic vaccines have also emerged as a promising treatment strategy to induce robust humoral responses by activating B cells. For example, the ferritin nanoparticle vaccine that delivers preS1 to specific myeloid cells, including $SIGNR1^+$ dendritic cells, that activate Tfh cells and lymphatic sinus-associated $SIGNR1^+$ macrophages that can activate B cells.[108] Furthermore, a recent study developed a B cell epitope-based vaccine, which was able to suppress serum HBsAg and HBV DNA by inducing SEQ13-specific antibody response.[109]

Conclusion

During the pathogenesis of CHB, defective HBV-specific B cells and antibodies were identified, in which global B cells were dysfunctional; whereas, HBV-specific antibodies were found to be insufficient and might be functionally limited. Tfh cells residing in peripheral blood, spleen and liver are pivotal to facilitate the seroconversion of HBeAg and HBsAg. Novel hepatitis B treatment strategies targeting B cells might facilitate the recovery of B cell function and develop the desired B cell responses, leading to functional cure of CHB.

Funding

This work was supported by National Natural Science Foundation of China (82002133 and 81600201) Nanjing Medical Science and Technique Development Foundation (QRX17141), Nanjing Department of Health (YKK19056 and YKK19078), and Yangzhou Key R&D Program (Social Development) (YZ2020101), Jiangsu Provincial Commission of Health and Family Planning (Q2017003).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study conception and design (YC, CW, SY), drafted the first version of the manuscript (YL, RI), edited and revised the manuscript (SY, YC, YL, GW, GC, RI,DW, GC, RH,XT,JX,CC). All authors approved the final version of the article, including the authorship list.

References

[1] Hepatitis B virus infection. Nat Rev Dis Primers 2018;4:18036. doi:10.1038/nrdp.2018.36.
[2] Chu CM, Liaw YF. Hepatitis B surface antigen seroclearance during chronic HBV infection. Antivir Ther 2010;15(2):133–143. doi:10.3851/IMP1497.
[3] Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48(2):335–352. doi:10.1016/j.jhep.2007.11.011.
[4] Konerman MA, Lok AS. Interferon treatment for hepatitis B. Clin Liver Dis 2016;20(4):645–665. doi:10.1016/j.cld.2016.06.002.
[5] Lazarus JV, Sperle I, Safreed-Harmon K, Gore C, Cebolla B, Spina A. Associations between national viral hepatitis policies/programmes and country-level socioeconomic factors: a sub-analysis of data from the 2013 WHO viral hepatitis policy report. BMC Public Health 2017;18(1):16. doi:10.1186/s12889-017-4549-4.
[6] Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373(9663):582–592. doi:10.1016/S0140-6736(09)60207-5.
[7] Cornberg M, Lok AS, Terrault NA, Zoulim F, Faculty E-AHTEC. Guidance for design and endpoints of clinical trials in chronic hepatitis B - report from the 2019 EASL-AASLD HBV treatment endpoints conference (double dagger). J Hepatol 2020;72(3):539–557. doi:10.1016/j.jhep.2019.11.003.
[8] Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: From discovery to regulatory approval. J Hepatol 2017;67(4):847–861. doi:10.1016/j.jhep.2017.05.008.

[9] Pan CQ, Li MH, Yi W, Zhang L, Lu Y, Hao HX, *et al*. Outcome of Chinese patients with hepatitis B at 96 weeks after functional cure with IFN versus combination regimens. Liver Int 2021. doi:10.1111/liv.14801.
[10] Lee HM, Banini BA. Updates on chronic HBV: current challenges and future goals. Curr Treat Options Gastroenterol 2019;17(2):271–291. doi:10.1007/s11938-019-00236-3.
[11] Liang LY, Wong GL. Unmet need in chronic hepatitis B management. Clin Mol Hepatol 2019;25(2):172–180. doi:10.3350/cmh.2018.0106.
[12] Feng J, Lu L, Hua C, Qin L, Zhao P, Wang J, *et al*. High frequency of CD4+ CXCR5+ TFH cells in patients with immune-active chronic hepatitis B. PLoS One 2011;6(7):e21698. doi:10.1371/journal.pone.0021698.
[13] Gold Y, Somech R, Mandel D, Peled Y, Reif S. Decreased immune response to hepatitis B eight years after routine vaccination in Israel. Acta Paediatr 2003;92(10):1158–1162. doi:10.1080/08035250310005756.
[14] Chaudhari CN, Bhagat MR, Shah T, Misra RN. Antibody to hepatitis B surface antigen in vaccinated health care workers. Med J Armed Forces India 2008;64(4):329–332. doi:10.1016/S0377-1237(08)80013-5.
[15] Dentico P, Buongiorno R, Volpe A, Zavoianni A, Pastore G, Schiraldi O. Long-term immunogenicity safety and efficacy of a recombinant hepatitis B vaccine in healthy adults. Eur J Epidemiol 1992;8(5):650–655. doi:10.1007/bf00145379.
[16] Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014;384 (9959):2053–2063. doi:10.1016/S0140-6736(14)60220-8.
[17] Raimondo G, Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. J Hepatol 2007;46(1):160–170. doi:10.1016/j.jhep.2006.10.007.
[18] Alderson P, Ritchie S, Kingsmill S. Cancer support groups: a friend at hand. Nurs Stand 1989;3(23):30–32. doi:10.7748/ns.3.23.30.s47.
[19] Xu X, Shang Q, Chen X, Nie W, Zou Z, Huang A, *et al*. Reversal of B-cell hyperactivation and functional impairment is associated with HBsAg seroconversion in chronic hepatitis B patients. Cell Mol Immunol 2015;12(3):309–316. doi:10.1038/cmi.2015.25.
[20] Schilling R, Ijaz S, Davidoff M, Lee JY, Locarnini S, Williams R, *et al*. Endocytosis of hepatitis B immune globulin into hepatocytes inhibits the secretion of hepatitis B virus surface antigen and virions. J Virol 2003;77(16):8882–8892. doi:10.1128/jvi.77.16.8882-8892.2003.
[21] Spaan M, Bruce M, Agarwal K, Carey I. The role of anti-HBs in hepatitis B reactivation during direct-acting antiviral therapy for chronic hepatitis C. Antivir Ther 2018;23(6):539–542. doi:10.3851/IMP3259.
[22] Outlaw MC, Dimmock NJ. IgG neutralization of type A influenza viruses and the inhibition of the endosomal fusion stage of the infectious pathway in BHK cells. Virology 1993;195(2):413–421. doi:10.1006/viro.1993.1391.
[23] Shouval D, Wands JR, Zurawski VR Jr, Isselbacher KJ, Shafritz DA. Selecting binding and complement-mediated lysis of human hepatoma cells (PLC/PRF/5) in culture by monoclonal antibodies to hepatitis B surface antigen. Proc Natl Acad Sci U S A 1982;79(2):650–654. doi:10.1073/pnas.79.2.650.
[24] Su YC, Lin PC, Yu HC, Wu CC. Hepatitis B virus reactivation in patients with resolved hepatitis B virus infection receiving chemotherapy or immunosuppressive therapy. Eur J Gastroenterol Hepatol 2018;30(8):925–929. doi:10.1097/MEG.0000000000001130.
[25] Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, *et al*. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27(4):605–611. doi:10.1200/JCO.2008.18.0182.
[26] Nishida T, Matsubara T, Yakushijin T, Inada M. Prediction and clinical implications of HBV reactivation in lymphoma patients with resolved HBV infection: focus on anti-HBs and anti-HBc antibody titers. Hepatol Int 2019;13(4):407–415. doi:10.1007/s12072-019-09966-z.
[27] Schumann A, Lindemann M, Valentin-Gamazo C, Lu M, Elmaagacli A, Dahmen U, *et al*. Adoptive immune transfer of hepatitis B virus specific immunity from immunized living liver donors to liver recipients. Transplantation 2009;87(1):103–111. doi:10.1097/TP.0b013e31818bfc85.
[28] Li D, He W, Liu X, Zheng S, Qi Y, Li H, *et al*. A potent human neutralizing antibody Fc-dependently reduces established HBV infections. Elife 2017;6:e26738. doi:10.7554/eLife.26738.
[29] Hehle V, Beretta M, Bourgine M, Ait-Goughoulte M, Planchais C, Morisse S, *et al*. Potent human broadly neutralizing antibodies to hepatitis B virus from natural controllers. J Exp Med 2020;217(10):e20200840. doi:10.1084/jem.20200840.
[30] Zhang TY, Yuan Q, Zhao JH, Zhang YL, Yuan LZ, Lan Y, *et al*. Prolonged suppression of HBV in mice by a novel antibody that targets a unique epitope on hepatitis B surface antigen. Gut 2016;65(4):658–671. doi:10.1136/gutjnl-2014-308964.
[31] Zankharia US, Kudchodkar S, Khoshnejad M, Perales-Puchalt A, Choi H, Ho M, *et al*. Neutralization of hepatitis B virus by a novel DNA-encoded monoclonal antibody. Hum Vaccin Immunother 2020;16(9):2156–2164. doi:10.1080/21645515.2020.1763686.
[32] Lazdina U, Alheim M, Nystrom J, Hultgren C, Borisova G, Sominskaya I, *et al*. Priming of cytotoxic T cell responses to exogenous hepatitis B virus core antigen is B cell dependent. J Gen Virol 2003;84(Pt 1):139–146. doi:10.1099/vir.0.18678-0.
[33] Abbas AK, Haber S, Rock KL. Antigen presentation by hapten-specific B lymphocytes. II. Specificity and properties of antigen-presenting B lymphocytes, and function of immunoglobulin receptors. J Immunol 1985;135(3):1661–1667.
[34] Lanzavecchia A. Antigen-specific interaction between T and B cells. Nature 1985;314(6011):537–539. doi:10.1038/314537a0.
[35] Chesnut RW, Grey HM. Studies on the capacity of B cells to serve as antigen-presenting cells. J Immunol 1981;126(3):1075–1079.
[36] Tony HP, Phillips NE, Parker DC. Role of membrane immunoglobulin (Ig) crosslinking in membrane Ig-mediated, major histocompatibility-restricted T cell-B cell cooperation. J Exp Med 1985;162(5):1695–1708. doi:10.1084/jem.162.5.1695.
[37] Jin Y, Shih WK, Berkower I. Human T cell response to the surface antigen of hepatitis B virus (HBsAg). Endosomal and nonendosomal processing pathways are accessible to both endogenous and exogenous antigen. J Exp Med 1988;168(1):293–306. doi:10.1084/jem.168.1.293.
[38] Schirmbeck R, Reimann J. Enhancing the immunogenicity of exogenous hepatitis B surface antigen-based vaccines for MHC-I-restricted T cells. Biol Chem 1999;380(3):285–291. doi:10.1515/BC.1999.039.
[39] Tian C, Chen Y, Liu Y, Wang S, Li Y, Wang G, *et al*. Use of ELISpot assay to study HBs-specific B cell responses in vaccinated and HBV infected humans. Emerg Microbes Infect 2018;7(1):16. doi:10.1038/s41426-018-0034-0.
[40] Cannons JL, Lau P, Ghumman B, DeBenedette MA, Yagita H, Okumura K, *et al*. 4-1BB ligand induces cell division, sustains survival, and enhances effector function of CD4 and CD8 T cells with similar efficacy. J Immunol 2001;167(3):1313–1324. doi:10.4049/jimmunol.167.3.1313.
[41] Liu Y, Wang G, Chen Y, Huang R, Tian C, Li Y, *et al*. HBcAg-induced upregulated 4-1BB ligand on B cells contributes to B-cell hyperactivation during chronic hepatitis B infection. J Med Virol 2019;91(5):781–790. doi:10.1002/jmv.25377.
[42] Bertoletti A, Ferrari C. Adaptive immunity in HBV infection. J Hepatol 2016;64(1 Suppl):S71–S83. doi:10.1016/j.jhep.2016.01.026.
[43] Salimzadeh L, Le Bert N, Dutertre CA, Gill US, Newell EW, Frey C, *et al*. PD-1 blockade partially recovers dysfunctional virus-specific B cells in chronic hepatitis B infection. J Clin Invest 2018;128(10):4573–4587. doi:10.1172/JCI121957.
[44] Wang L, Qiu J, Yu L, Hu X, Zhao P, Jiang Y. Increased numbers of CD5 +CD19+CD1dhighIL-10+ Bregs, CD4+Foxp3+ Tregs, CD4+CXCR5+Foxp3+ follicular regulatory T (TFR) cells in CHB or CHC patients. J Transl Med 2014;12:251. doi:10.1186/s12967-014-0251-9.
[45] Westhoff TH, Jochimsen F, Schmittel A, Stoffler-Meilicke M, Schafer JH, Zidek W, *et al*. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. Blood 2003;102(5):1930. doi:10.1182/blood-2003-05-1403.
[46] Heim MH, Thimme R. Innate and adaptive immune responses in HCV infections. J Hepatol 2014;61(1 Suppl):S14–25. doi:10.1016/j.jhep.2014.06.035.
[47] Bocher WO, Herzog-Hauff S, Herr W, Heermann K, Gerken G, Meyer Zum Buschenfelde KH, *et al*. Regulation of the neutralizing anti-hepatitis B surface (HBs) antibody response in vitro in HBs vaccine recipients and patients with acute or chronic hepatitis B virus (HBV) infection. Clin Exp Immunol 1996;105(1):52–58. doi:10.1046/j.1365-2249.1996.d01-732.x.
[48] Moir S, Fauci AS. Pathogenic mechanisms of B-lymphocyte dysfunction in HIV disease. J Allergy Clin Immunol 2008;122(1):12–19; quiz 20-21. doi:10.1016/j.jaci.2008.04.034.
[49] Moir S, Fauci AS. B cells in HIV infection and disease. Nat Rev Immunol 2009;9(4):235–245. doi:10.1038/nri2524.
[50] Zhang Z, Zou ZS, Fu JL, Cai L, Jin L, Liu YJ, *et al*. Severe dendritic cell perturbation is actively involved in the pathogenesis of acute-on-chronic hepatitis B liver failure. J Hepatol 2008;49(3):396–406. doi:10.1016/j.jhep.2008.05.017.
[51] Zhou SN, Zhang N, Liu HH, Xia P, Zhang C, Song JW, *et al*. Skewed CD39/CD73/adenosine pathway contributes to B-cell hyperactivation and disease progression in patients with chronic hepatitis B. Gastroenterol Rep (Oxf) 2020;9(1):49–58. doi:10.1093/gastro/goaa048.
[52] Huang J, Doria-Rose NA, Longo NS, Laub L, Lin CL, Turk E, *et al*. Isolation of human monoclonal antibodies from peripheral blood B cells. Nat Protoc 2013;8(10):1907–1915. doi:10.1038/nprot.2013.117.
[53] Barnaba V, Valesini G, Levrero M, Zaccari C, Van Dyke A, Falco M, *et al*. Immunoregulation of the in vitro anti-HBs antibody synthesis in chronic HBsAg carriers and in recently boosted anti-hepatitis B vaccine recipients. Clin Exp Immunol 1985;60(2):259–266.
[54] Lee J, Dollins CM, Boczkowski D, Sullenger BA, Nair S. Activated B cells modified by electroporation of multiple mRNAs encoding immune stimulatory molecules are comparable to mature dendritic cells in inducing in vitro antigen-specific T-cell responses. Immunology 2008;125(2):229–240. doi:10.1111/j.1365-2567.2008.02833.x.
[55] Pollok KE, Kim YJ, Hurtado J, Zhou Z, Kim KK, Kwon BS. 4-1BB T-cell antigen binds to mature B cells and macrophages, and costimulates anti-mu-primed splenic B cells. Eur J Immunol 1994;24(2):367–374. doi:10.1002/eji.1830240215.
[56] Knox JJ, Kaplan DE, Betts MR. T-bet-expressing B cells during HIV and HCV infections. Cell Immunol 2017;321:26–34. doi:10.1016/j.cellimm.2017.04.012.
[57] Barnett BE, Staupe RP, Odorizzi PM, Palko O, Tomov VT, Mahan AE, *et al*. Cutting edge: B cell-intrinsic T-bet expression is required to control chronic viral infection. J Immunol 2016;197(4):1017–1022. doi:10.4049/jimmunol.1500368.
[58] Rubtsova K, Rubtsov AV, van Dyk LF, Kappler JW, Marrack P. T-box transcription factor T-bet, a key player in a unique type of B-cell activation essential for effective viral clearance. Proc Natl Acad Sci U S A 2013;110(34):E3216–3224. doi:10.1073/pnas.1312348110.
[59] Wang NS, McHeyzer-Williams LJ, Okitsu SL, Burris TP, Reiner SL, McHeyzer-Williams MG. Divergent transcriptional programming of class-specific B cell memory by T-bet and RORalpha. Nat Immunol 2012;13(6):604–611. doi:10.1038/ni.2294.
[60] Blair PA, Norena LY, Flores-Borja F, Rawlings DJ, Isenberg DA, Ehrenstein MR, *et al*. CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic Lupus Erythematosus patients. Immunity 2010;32(1):129–140. doi:10.1016/j.immuni.2009.11.009.

[61] Ding Q, Yeung M, Camirand G, Zeng Q, Akiba H, Yagita H, *et al*. Regulatory B cells are identified by expression of TIM-1 and can be induced through TIM-1 ligation to promote tolerance in mice. J Clin Invest 2011; 121(9):3645–3656. doi:10.1172/JCI46274.
[62] Barreiro P, Vispo E, Poveda E, Fernandez-Montero JV, Soriano V. Hepatitis C therapy: highlights from the 2012 annual meeting of the European Association for the Study of the Liver. Clin Infect Dis 2013;56(4):560–566. doi:10.1093/cid/cis915.
[63] Wang G, Liu Y, Huang R, Jia B, Su R, Sun Z, *et al*. Characteristics of regulatory B cells in patients with chronic hepatitis B virus infection in different immune phases. Discov Med 2017;23(128):295–304.
[64] Sarvaria A, Madrigal JA, Saudemont A. B cell regulation in cancer and anti-tumor immunity. Cell Mol Immunol 2017;14(8):662–674. doi:10.1038/cmi.2017.35.
[65] Couper KN, Blount DG, Riley EM. IL-10: the master regulator of immunity to infection. J Immunol 2008;180(9):5771–5777. doi:10.4049/jimmunol.180.9.5771.
[66] Dunn C, Peppa D, Khanna P, Nebbia G, Jones M, Brendish N, *et al*. Temporal analysis of early immune responses in patients with acute hepatitis B virus infection. Gastroenterology 2009;137(4):1289–1300. doi:10.1053/j.gastro.2009.06.054.
[67] Peppa D, Micco L, Javaid A, Kennedy PT, Schurich A, Dunn C, *et al*. Blockade of immunosuppressive cytokines restores NK cell antiviral function in chronic hepatitis B virus infection. PLoS Pathog 2010;6(12):e1001227. doi:10.1371/journal.ppat.1001227.
[68] Tan AT, Koh S, Goh W, Zhe HY, Gehring AJ, Lim SG, *et al*. A longitudinal analysis of innate and adaptive immune profile during hepatic flares in chronic hepatitis B. J Hepatol 2010;52(3):330–339. doi:10.1016/j.jhep.2009.12.015.
[69] Mizoguchi A, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. Immunity 2002;16(2):219–230. doi:10.1016/s1074-7613(02)00274-1.
[70] Mauri C, Gray D, Mushtaq N, Londei M. Prevention of arthritis by interleukin 10-producing B cells. J Exp Med 2003;197(4):489–501. doi:10.1084/jem.20021293.
[71] Le Bert N, Salimzadeh L, Gill US, Dutertre CA, Facchetti F, Tan A, *et al*. Comparative characterization of B cells specific for HBV nucleocapsid and envelope proteins in patients with chronic hepatitis B. J Hepatol 2020;72(1):34–44. doi:10.1016/j.jhep.2019.07.015.
[72] Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol 2011; 29:621–663. doi:10.1146/annurev-immunol-031210-101400.
[73] King C, Tangye SG, Mackay CR. T follicular helper (TFH) cells in normal and dysregulated immune responses. Annu Rev Immunol 2008;26:741–766. doi:10.1146/annurev.immunol.26.021607.090344.
[74] Victora GD, Nussenzweig MC. Germinal centers. Annu Rev Immunol 2012;30:429–457. doi:10.1146/annurev-immunol-020711-075032.
[75] Gharibi T, Hosseini A, Marofi F, Oraei M, Jahandideh S, Abdollahpour-Alitappeh M, *et al*. IL-21 and IL-21-producing T cells are involved in multiple sclerosis severity and progression. Immunol Lett 2019;216:12–20. doi:10.1016/j.imlet.2019.09.003.
[76] Paulos CM, Carpenito C, Plesa G, Suhoski MM, Varela-Rohena A, Golovina TN, *et al*. The inducible costimulator (ICOS) is critical for the development of human T(H)17 cells. Sci Transl Med 2010;2(55):55ra78. doi:10.1126/scitranslmed.3000448.
[77] Bentebibel SE, Schmitt N, Banchereau J, Ueno H. Human tonsil B-cell lymphoma 6 (BCL6)-expressing CD4+ T-cell subset specialized for B-cell help outside germinal centers. Proc Natl Acad Sci U S A 2011;108(33):E488–497. doi:10.1073/pnas.1100898108.
[78] Wang Y, Wang L, Shi Y, Wang F, Yang H, Han S, *et al*. Altered circulating T follicular helper cell subsets in patients with psoriasis vulgaris. Immunol Lett 2017;181:101–108. doi:10.1016/j.imlet.2016.09.008.
[79] Bentebibel SE, Lopez S, Obermoser G, Schmitt N, Mueller C, Harrod C, *et al*. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. Sci Transl Med 2013;5(176):176ra132. doi:10.1126/scitranslmed.3005191.
[80] Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, *et al*. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. Immunity 2011;34(1):108–121. doi:10.1016/j.immuni.2010.12.012.
[81] Figueiredo MM, Costa PAC, Diniz SQ, Henriques PM, Kano FS, Tada MS, *et al*. T follicular helper cells regulate the activation of B lymphocytes and antibody production during Plasmodium vivax infection. PLoS Pathog 2017;13(7):e1006484. doi:10.1371/journal.ppat.1006484.
[82] Obeng-Adjei N, Portugal S, Tran TM, Yazew TB, Skinner J, Li S, *et al*. Circulating Th1-cell-type Tfh cells that exhibit impaired B cell help are preferentially activated during acute malaria in children. Cell Rep 2015;13(2):425–439. doi:10.1016/j.celrep.2015.09.004.
[83] Miles B, Connick E. TFH in HIV latency and as sources of replication-competent virus. Trends Microbiol 2016;24(5):338–344. doi:10.1016/j.tim.2016.02.006.
[84] Rappuoli R, Aderem A. A 2020 vision for vaccines against HIV, tuberculosis and malaria. Nature 2011;473(7348):463–469. doi:10.1038/nature10124.
[85] He R, Hou S, Liu C, Zhang A, Bai Q, Han M, *et al*. Follicular CXCR5- expressing CD8(+) T cells curtail chronic viral infection. Nature 2016;537(7620):412–428. doi:10.1038/nature19317.
[86] Hu TT, Song XF, Lei Y, Hu HD, Ren H, Hu P. Expansion of circulating TFH cells and their associated molecules: involvement in the immune landscape in patients with chronic HBV infection. Virol J 2014;11:54. doi:10.1186/1743-422X-11-54.
[87] Zhang L, Zhang M, Li H, Chen Z, Luo A, Liu B, *et al*. Tfh cell-mediated humoral immune response and HBsAg level can predict HBeAg seroconversion in chronic hepatitis B patients receiving peginterferon-alpha therapy. Mol Immunol 2016;73:37–45. doi:10.1016/j.molimm.2016.03.011.
[88] Yanaba K, Bouaziz JD, Haas KM, Poe JC, Fujimoto M, Tedder TF. A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. Immunity 2008;28(5):639–650. doi:10.1016/j.immuni.2008.03.017.
[89] Li Y, Tang L, Guo L, Chen C, Gu S, Zhou Y, *et al*. CXCL13-mediated recruitment of intrahepatic CXCR5(+)CD8(+) T cells favors viral control in chronic HBV infection. J Hepatol 2020;72(3):420–430. doi:10.1016/j.jhep.2019.09.031.
[90] Shen J, Luo X, Wu Q, Huang J, Xiao G, Wang L, *et al*. A subset of CXCR5(+) CD8(+) T cells in the germinal centers from human tonsils and lymph nodes help B cells produce immunoglobulins. Front Immunol 2018;9:2287. doi:10.3389/fimmu.2018.02287.
[91] Wang R, Xie R, Song Z. Circulating regulatory Tfh cells are enriched in patients with chronic hepatitis B infection and induce the differentiation of regulatory B cells. Exp Cell Res 2018;365(2):171–176. doi:10.1016/j.yexcr.2018.02.031.
[92] Wang X, Dong Q, Li Q, Li Y, Zhao D, Sun J, *et al*. Dysregulated response of follicular helper T cells to hepatitis B surface antigen promotes HBV persistence in mice and associates with outcomes of patients. Gastroenterology 2018;154(8):2222–2236. doi:10.1053/j.gastro.2018.03.021.
[93] Xu L, Yin W, Sun R, Wei H, Tian Z. Liver type I regulatory T cells suppress germinal center formation in HBV-tolerant mice. Proc Natl Acad Sci U S A 2013;110(42):16993–16998. doi:10.1073/pnas.1306437110.
[94] Xu F, Song H, Xiao Q, Li N, Zhang H, Cheng G, *et al*. Type III interferon-induced CBFbeta inhibits HBV replication by hijacking HBx. Cell Mol Immunol 2019;16(4):357–366. doi:10.1038/s41423-018-0006-2.
[95] Chen X, Chen X, Chen W, Ma X, Huang J, Chen R. Extended peginterferon alfa-2a (Pegasys) therapy in Chinese patients with HBeAg-negative chronic hepatitis B. J Med Virol 2014;86(10):1705–1713. doi:10.1002/jmv.24013.
[96] Chen X, Mao Q, Xie Y, Dou X, Xie Q, Sheng J, *et al*. A potential functional cure in Chinese HBeAg-negative chronic hepatitis B patients treated with peg-interferon alpha-2a. J Clin Transl Hepatol 2019;7(3):249–257. doi:10.14218/JCTH.2019.00016.
[97] European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57(1):167–185. doi:10.1016/j.jhep.2012.02.010.
[98] Xue R. Pegasys and ribavirin therapy in an elderly patient with chronic hepatitis C. Zhonghua Gan Zang Bing Za Zhi 2011;19(8):627–628. doi:10.3760/cma.j.issn.1007-3418.2011.08.018.
[99] Micco L, Peppa D, Loggi E, Schurich A, Jefferson L, Cursaro C, *et al*. Differential boosting of innate and adaptive antiviral responses during pegylated-interferon-alpha therapy of chronic hepatitis B. J Hepatol 2013;58(2):225–233. doi:10.1016/j.jhep.2012.09.029.
[100] Liu YZ, Hou FQ, Ding P, Ren YY, Li SH, Wang GQ. Pegylated interferon alpha enhances recovery of memory T cells in e antigen positive chronic hepatitis B patients. Virol J 2012;9:274. doi:10.1186/1743-422X-9-274.
[101] Stelma F, de Niet A, Tempelmans Plat-Sinnige MJ, Jansen L, Takkenberg RB, Reesink HW, *et al*. Natural killer cell characteristics in patients with chronic hepatitis B virus (HBV) infection are associated with HBV surface antigen clearance after combination treatment with pegylated interferon alfa-2a and adefovir. J Infect Dis 2015;212(7):1042–1051. doi:10.1093/infdis/jiv180.
[102] Rehermann B, Lau D, Hoofnagle JH, Chisari FV. Cytotoxic T lymphocyte responsiveness after resolution of chronic hepatitis B virus infection. J Clin Invest 1996;97(7):1655–1665. doi:10.1172/JCI118592.
[103] Aspord C, Bruder Costa J, Jacob MC, Dufeu-Duchesne T, Bertucci I, Pouget N, *et al*. Remodeling of B-cell subsets in blood during pegylated IFNalpha-2a therapy in patients with chronic hepatitis B infection. PLoS One 2016;11(6):e0156200. doi:10.1371/journal.pone.0156200.
[104] Kennedy MK, Willis CR, Armitage RJ. Deciphering CD30 ligand biology and its role in humoral immunity. Immunology 2006;118(2):143–152. doi:10.1111/j.1365-2567.2006.02354.x.
[105] Roethle PA, McFadden RM, Yang H, Hrvatin P, Hui H, Graupe M, *et al*. Identification and optimization of pteridinone Toll-like receptor 7 (TLR7) agonists for the oral treatment of viral hepatitis. J Med Chem 2013; 56(18):7324–7333. doi:10.1021/jm400815m.
[106] Li L, Barry V, Daffis S, Niu C, Huntzicker E, French DM, *et al*. Anti-HBV response to toll-like receptor 7 agonist GS-9620 is associated with intrahepatic aggregates of T cells and B cells. J Hepatol 2018;68(5):912–921. doi:10.1016/j.jhep.2017.12.008.
[107] Cooper CL, Davis HL, Morris ML, Efler SM, Adhami MA, Krieg AM, *et al*. CPG 7909, an immunostimulatory TLR9 agonist oligodeoxynucleotide, as adjuvant to Engerix-B HBV vaccine in healthy adults: a double-blind phase I/II study. J Clin Immunol 2004;24(6):693–701. doi:10.1007/s10875-004-6244-3.
[108] Wang W, Zhou X, Bian Y, Wang S, Chai Q, Guo Z, *et al*. Dual-targeting nanoparticle vaccine elicits a therapeutic antibody response against chronic hepatitis B. Nat Nanotechnol 2020;15(5):406–416. doi:10.1038/s41565-020-0648-y.
[109] Zhang TY, Guo XR, Wu YT, Kang XZ, Zheng QB, Qi RY, *et al*. A unique B cell epitope-based particulate vaccine shows effective suppression of hepatitis B surface antigen in mice. Gut 2020;69(2):343–354. doi:10.1136/gutjnl-2018-317725.