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Human immune repertoire in hepatitis B virus infection

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Abstract

Hepatitis B virus (HBV) infection is a public health threat that affects 257 million people worldwide and can progress to liver cirrhosis, liver failure, and hepatocellular carcinoma. The HBV antigen- induced adaptive immune response plays an important role in HBV clearance. Immune repertoire sequencing (IRS) has been used to investigate the molecular mechanisms behind the immune system, find novel ways to treat HBV infection, and evaluate the genetic responses and immune characteristics of individuals infected by HBV or immunized by HBV vaccine. This review summarizes the human immune repertoire analysis methodology, and the application of the IRS in the prediction of HBV infection progression, treatment, and vaccination.

Key Words: Immune repertoire; T-cell receptor; B-cell receptor; Hepatitis B virus; Chronic viral infection; High-throughput sequencing

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Core Tip: A Hepatitis B virus (HBV) cure depends on activation of the anti-HBV adaptive immune system. Immune repertoire sequencing is a novel method to investigate all aspects of the human adaptive immune system. However, the immune repertoire in HBV infection is still not clear. We review the immune repertoire analysis methodology and provide a new insight into outcomes of HBV infection and vaccination.

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INTRODUCTION

Hepatitis B virus (HBV) is a hepatotropic, small, enveloped DNA virus that belongs to the Hepadnaviridae family and causes an acute or chronic infection in humans. The duration of infection is variable, ranging from 8 weeks to over 6 months. Chronic hepatitis B (CHB) infection is more common clinically in patients whose immune system fail to fight against HBV, and is characterized by a high HBV DNA load and HBsAg seropositivity. It can lead to advanced liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC). CHB cannot be completely cured currently because of the existence of covalently closed circular DNA (cccDNA) in the cell nucleus, but it can be controlled by nucleos(t)ide analogs (NUCs) and interferon (IFN).

The immune response against HBV is the key to a cure, which involves both innate and adaptive immune responses. During acute infection, hepatocytes produce type 1 IFN, which inhibits viral packaging. The clearance of HBV is accompanied by asymptomatic or flulike symptoms[1]. Dysfunction and exhaustion of HBV-specific CD4+ and CD8+ T cells, decreased numbers and dysfunction of dendritic cells (DCs), nature killer (NK), and NKT cells are immune responses seen during CHB infection, as well as upregulated expression of immune molecules, including programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and mucin domain -3 (Tim³)[2-6]. Innate immune response are also downregulated during CHB infection, with dysfunction of toll-like receptors (TLRs)[7], which contribute to inducing a robust IFN response and suppressing HBV replication. In this review, we summarize the current state of knowledge of the immune repertoire and the relevance to understanding HBV infection (Table 1).

The immune repertoire includes the human T-cell receptors (TCRs) and B-cell receptors (BCRs) of the adaptive immune system. The generation of diverse TCRs expressed on the cell membrane of T lymphocytes and BCRs expressed by B lymphocytes maintain the balance of adaptive immunity and recognize the amounts of antigens. There are two types of T cells, $\alpha\beta$ T cells and $\gamma\delta$ T cells, according to their TCR genes. In $\alpha\beta$ T cells, the TCRs are composed of one alpha and one beta chain. In $\gamma\delta$ T cells, the TCRs consist of one gamma and one delta chain. The variable region of each chain consists of three complementarity-determining regions (CDRs), which are variable and determine the antigen specificity, and four frame regions (FRs). CDR1 and CDR2 are coded by variable (V) genes, and CDR3 is generated by random selection and recombination of variable (V), diversity (D), and joining (J) genes[8,9]. In all, the generation of diversity in TCR consists of a vast number of TCR gene segments recombinants, junction diversity, and alpha/beta or delta/gamma chain pairing during the development of T cells[10-12]. As for immunoglobulin (Ig) antibodies, BCR induces a Y-shaped protein composed of two large heavy chains encoded by the immunoglobulin gene heavy locus and two small light chains encoded by the immunoglobulin lambda locus (IGL) or immunoglobulin kappa locus (IGK). The heavy chain variable region is encoded by V, D, J gene families like those of T cells. The light chain is encoded by only V and J gene families. Before antigen stimulation, V(D)J recombination is mediated by several enzyme-like recombination-activating genes (RAG1/RAG2). Random additions and deletions of V-D and D-J (V-J for the light chain) joining regions contribute to the diversity of Ig[13,14]. The post antigen-stimulation response of Ig is more complicated, and includes somatic hypermutation, which is a programmed mutation process whereby changes are introduced to the nucleotide sequence of the immunoglobulin gene DNA during development[15]. The response also includes gene conversion, the asymmetrical segregation of genes during replication, which leads to the production of nonreciprocal recombinant strands and the apparent conversion of one allele into another[15]. Finally, class-switch recombination, B-lymphocyte gene rearrangement that results in substitution of the type of heavy chain constant region that is expressed and allows a change of the effector response while the antigen-binding specificity (*i.e.* the variable region) remains the same[15]. These three responses resulting in the functional differences of IgG, IgE, IgA, IgD, or IgM[16].

The ability of T cells and B cells to recognize and respond to their specific antigen is central to adaptive immunity. The fully functional antigen receptor complex with

Table 1 Immune repertoire investigation of hepatitis B virus infection

Number	Ref.	Patients	Amounts of samples	Repertoire	Sequencing reads	Tools
1	Deulofeut <i>et al</i> [59], 1997	2 volunteers	2	TCR repertoire	-	PRISM
2	Höhn <i>et al</i> [60], 2002	Healthy individuals immunized with recombinant hepatitis B surface antigen	7	TCR-VA and -VB repertoire in CD8+ T cells	-	FITC/PE
3	Soroosh <i>et al</i> [69], 2003	Nine healthy adult responders and six nonresponders	30	TCR beta chain variable gene		FRAGMENT MANAGER' software program
4	Yang <i>et al</i> [41], 2011	Forty-two patients with CSHB	42	TCR CDR3	-	SPSS 16.0 software
5	Xiong <i>et al</i> [44], 2014	18 patients with CSHB and 8 controls	26	TCR V β repertoire	-	DNAMAN software version 1.0
6	Han <i>et al</i> [52], 2015	Liver cancers and healthy adults	160	TCR CDR3	495708702	BLAST
7	Galson <i>et al</i> [62], 2015	Naïve group: <i>n</i> = 9; vaccine group: <i>n</i> = 9	108	B-cell repertoire	365863	R
8	Qu <i>et al</i> [37], 2016	4 CHB patients before and after HBeAg seroconversion	8	TCR V β repertoire	370210 to 685596	Homemade Perl script
9	Yang <i>et al</i> [55], 2016	12 HBeAg SC patients and 20 no HBeAg SC patients	96	TCRBV families	-	SPSS software version 19.0
10	Galson <i>et al</i> [63], 2016	9 healthy subjects	63	B-cell repertoire		R
11	Chang <i>et al</i> [70], 2016	4 pairs of HBeAg positive carrier and HBsAg negative non-carrier siblings	16	IgG immune repertoire	2.2 million	PEAR, Python, Numpy and SciPy, Ipython
12	Ma <i>et al</i> [64], 2017	3 healthy volunteers	6	IgM and IgG H chain CDR3 repertoires		IMGT/High V-Quest
13	Jiang <i>et al</i> [36], 2018	3 pairs of healthy identical twins and 7 pairs of chronic hepatitis B patients	20	CD8+ T-cell receptor beta (TCR β) chains	50 million	MIXCR
14	Yan <i>et al</i> [49], 2019	6 patients with HBV-related ACLF and 6 controls	12	BCR CDR3 region	An average number of 12243860.30 in the control group and an average number of 1229965.30 in the ACLF group	GraphPad Prism software
15	Miyasaka <i>et al</i> [61], 2019	5 volunteers	30	T-cell and B-cell receptor repertoire	TCR β chain repertoire was 153151 before HB vaccination, 180093 after the second HB vaccination, and 129044 the third HB vaccination; BCR IgG heavy (H) chain repertoires were 106664 before HB vaccination, 126237 after the second HB vaccination, and 135663 the third HB vaccination	SPSS software package, Easy R (EZR) version 1.37, GraphPad software package
16	Shen <i>et al</i> [48], 2020	5 HBV-ACLF	20	TCR repertoire	163259321	MIXCR
17	Lian <i>et al</i> [57], 2020	20 CHB patients undergoing 1-yr ETV treatment (10 HBeAg SC patients and 10 no HBeAg SC patients)	60	T-cell repertoire	-	MIXCR

ACLF: Acute-on-chronic liver failure; BCR: B-cell receptor; CDR3: Complementary determining region 3; CSHB: Chronic severe hepatitis B; ETV: Entecavir; HBV: Hepatitis B virus; Ig: Immunoglobulin. SC: Seroconversion; TCR: T-cell receptor.

coreceptors and costimulatory receptors on T cells and B cells has not only exquisite

antigen specificity but also different signaling pathways (Figure 1). The T-cell receptor complex consists of an antigen-binding TCR α and TCR β heterodimer associated with CD3 that has four signaling chains (two ϵ , one δ , and one γ), as well as a homodimer of ζ chains. Each CD3 chain has one tyrosine-based immunoreceptor activation motif (ITAM); each ζ chain has three. After a T cell has detected its specific antigen, phosphorylation of tyrosine residues in the ITAMs of the TCR enables binding of the cytosolic tyrosine kinase-zeta chain of the TCR-associated protein kinase 70 (ZAP-70), followed by the CD4 and CD8 coreceptors, which bind to major histocompatibility complex (MHC) class 2 molecules and class 1 molecules. Activated ZAP-70 leads to membrane recruitment of phospholipase C- γ (PLC- γ), which initiates three important signaling pathways that involve activation of nuclear factor of activated T cells (NFAT), nuclear factor kappa B (NF- κ B), and activator protein-1 (AP-1). Antigen detection thus results in the differentiation and proliferation that characterize the immune response[17,18]. The BCR complex includes cell-surface immunoglobulin with one each of the invariant signaling proteins, Ig α and Ig β , each of which has a single ITAM in their cytosolic tails that enables signal initiation after the BCR binds to an antigen. The logic of BCR signaling is similar to that of TCR signaling, but some of the signaling components are specific to B cells. When BCRs have bound a multivalent antigen, which cross-links them, three protein tyrosine kinases of the Src-family, Fyn, Blk, and Lyn, are activated and phosphorylate the ITAM tyrosine residues, which creates binding sites for the cytosolic protein, kinase spleen-associated tyrosine kinase (Syk). Syk then phosphorylates and activate the enzyme PLC- γ , which then initiates signaling pathways just as occurs with TCRs[19,20].

IMMUNE REPERTOIRE ANALYSIS METHODOLOGY

High-throughput sequencing (HTS) has increased the range, complexity, sensitivity, and accuracy with a great increase in the scale of operation, the number of nucleotides, and the number of copies of each nucleotide sequenced[15]. Investigation of the immune repertoire has thus become more effective, convenient, and less costly. The depth and amount of sequencing data obtained from of disease-specific TCR or BCR clones provide investigators with a great chance to identify individualized and common clonality during HBV infection. There are five phases of immune repertoire analysis starting with cell isolation or tissue collection (Figure 2). After collecting patient samples (cells and/or clots), DNA or mRNA is extracted, purified, and sequenced. DNA, is more suitable for calculating the proportions of antigen-specific T or B cells and for studying the functional/phenotypic evolution of specific TCR/BCR clonotypes. Therefore, it is recommended to choose mRNA to study cell function and activation[21].

It is important to complete the library preparation and amplification as that affects the accuracy of sequencing data. Two next-generation sequencing (NGS)-based amplification methods are currently applied. Multiplex PCR is the most convenient and straightforward approach for DNA samples. Because the V segment is highly variable, multiplex PCR incorporates V and J gene [constant (C) gene for mRNA] specific multiplex primers to amplify the full recombined variable region or CDR3 region of TCR/BCR gene[22,23]. PCR with the 5' RACE method for rapid amplification of cDNA ends, which only works with mRNA, but can theoretically avoid V gene bias. RNA is reverse transcribed with a gene-specific primer targeting a known 3' end sequence. The 5' end of an unknown sequence is amplified with a synthetic oligonucleotide[24,25]. Other methods like anchored multiplex PCR (AMP) introduced by Zheng *et al*[26] and TCR ligation-anchored-magnetically captured PCR (TCR-LA-MC PCR) introduced by Ruggiero *et al*[27] are designed to avoid amplification bias and sequencing sensitivity.

The fourth phase of immune repertoire is sequencing with HTS, which has been used since 2009. The most widely used HTS platforms are the Roche 454 sequencing system and the Illumina HiSeq platform. The Roche 454 sequencing system was the first HTS platform. It provides an average 500 bp read length per run and sequences millions of molecules per repertoire[28]. The Illumina HiSeq platform provides a shorter read length but significantly higher read throughput and a lower cost per read compared with the Roche 454, which cater to the demand of deep sequence of the complex immune repertoire[20,29].

The fifth phase is analyzing the TCR and BCR sequence data with appropriate bioinformatic tools. Many computational tools are available to analyze HTS data including IMGT/High V-QUEST[30], new IgBLAST[31], Decombinator[32], pRESTO

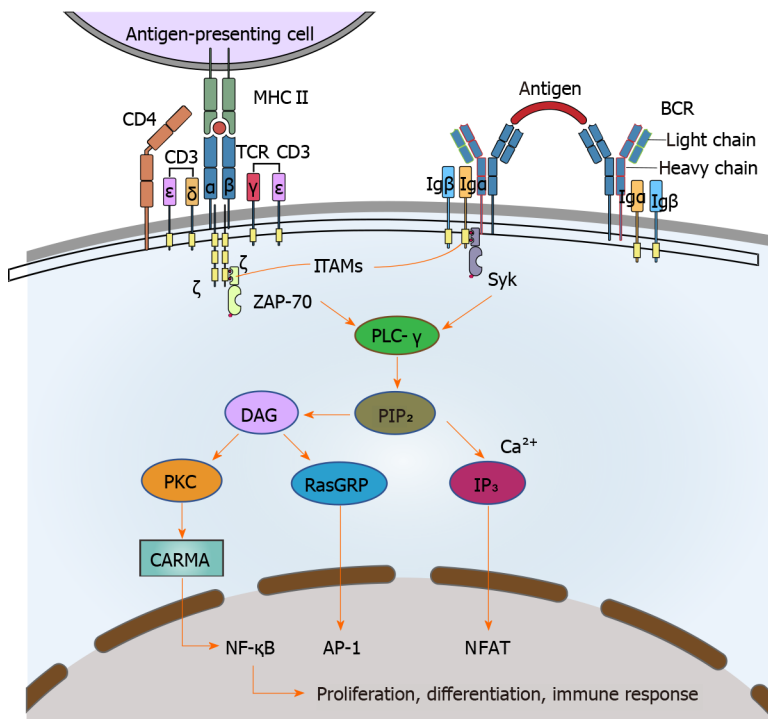


Figure 1 T-cell receptor and B-cell receptor structure and signaling pathways. T-cell receptor and B-cell receptor complexes include both variable antigen-recognition proteins and invariant signaling proteins. Phosphorylation of the ITAMs in CD3 ϵ , γ , δ , and the ζ chain enables them to bind the cytosolic tyrosine kinase ZAP-70, which in turn recruits and activates PLC- γ . Activated PLC- γ cleaves PIP₂ to yield DAG and IP₃. IP₃ increases intracellular Ca²⁺ concentration, activating calcineurin, a phosphatase that then activates an NFAT transcription factor. DAG recruits PKC to activate CARMA, which leads to activation of NF- κ B and recruits RasGRP, which activates AP-1. These three important signaling pathways activate transcription factors in the nucleus, including NF- κ B, NFAT, and AP-1, which result in cell differentiation, proliferation, and immune response. AP-1: Activator protein-1; CARMA: Caspase recruitment domain family, member 14 protein; DAG: Diacylglycerol; IP₃: Inositol trisphosphate; ITAM: Immunoreceptor tyrosine-based activation motif; NFAT: Nuclear factor of activated T cells; NF- κ B: Nuclear factor kappa B; PIP₂: Phosphatidylinositol bisphosphate; PKC: Protein kinase C; PLC- γ : Phospholipase C- γ ; RasGRP: RAS guanyl releasing protein; Syk: Spleen-associated tyrosine kinase; ZAP-70: Zeta chain of T-cell receptor-associated protein kinase 70.

[33], and MiXCR[34]. These bioinformatic tools can be used for VDJ gene assignment, CDR and FR annotation, CDR3 length identification, insertion and deletion analysis, and mutation spectrum analysis. What's more, the international immunogenetics information system (ImMunoGeneTics database) also provides important information about specific BCR and TCR V, D, J, and C genes[35].

CHARACTERISTICS OF THE IMMUNE REPERTOIRE IN HBV INFECTION PROGRESSION

Chronic HBV infections can persist with an asymptomatic carrier status or as chronic hepatitis B (CHB) that can progress to chronic severe hepatitis B (CSHB), cirrhosis, HBV-related acute-on-chronic liver failure (HBV-ACLF), and HCC. The progression of HBV infection is associated with the immune response, especially the adaptive immune response. The characteristics of the immune repertoire in HBV infection progression involve both TCRs and BCRs. Hepatitis B e antigen (HBeAg) seroconversion is an important step toward achieving a CHB cure, which appears to be dependent on an immune response to clear the virus. Jiang *et al*[36] analyzed CD8⁺ T-cell receptor beta (TCR β) chains in seven pairs of monozygotic twins with CHB and three healthy control pairs by HTS. Six pairs were infected with HBV during childhood; four of the six pairs had the same clinical outcomes. A high level of similarity in the TCR repertoire of each pair was found in average TCR V β segment expression and the frequency of the CDR3 pattern and skewed or oligoclonal clonotypes. Notably, the detailed CDR3 pattern and frequency were related to disease prognosis. There was an increased abundance of immunodominant clonotypes in patients with HBV antigen seroconversion[35]. Analysis of the TCR β chain repertoire in PBMCs from four CHB patients with HBeAg seroconversion demonstrated that TRBV β 12-4, V β 28, J β 2-1, V7-2-01-J2-1, V12-4-J1-1, and V28-1-J1-5 were associated with the development and treatment of CHB. No significant changes were observed following seroconversion

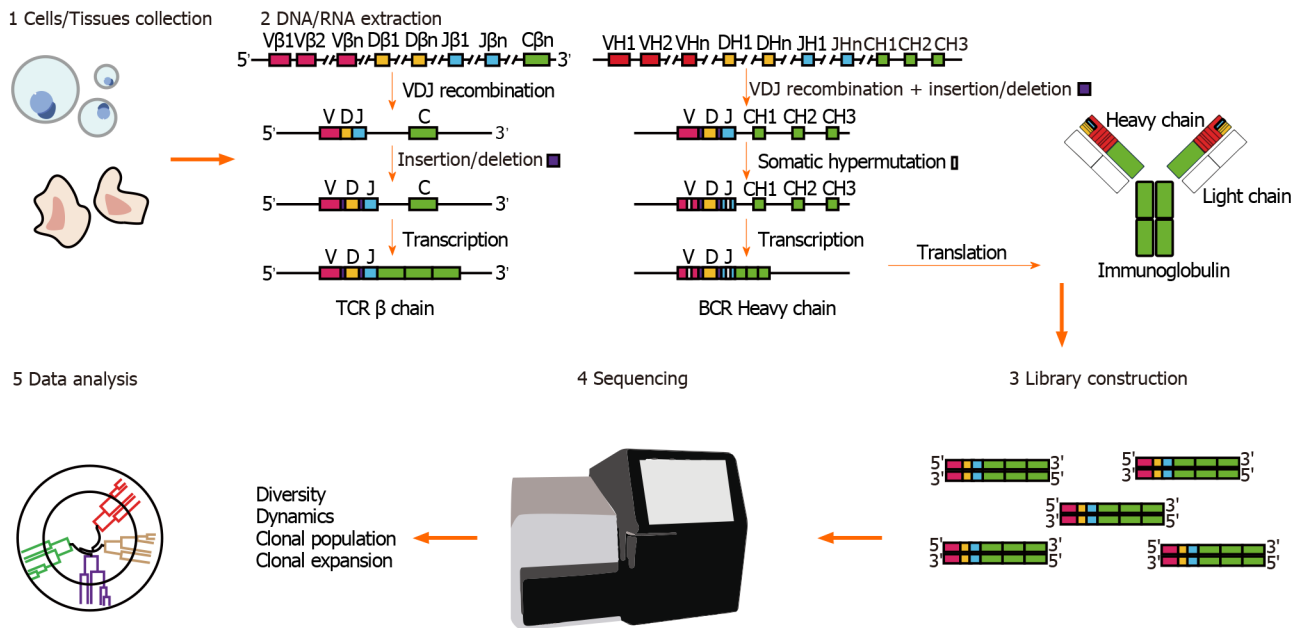


Figure 2 Workflow for immune repertoire sequencing. There are mainly five sections in immune repertoire analysis. 1: Cell/tissue collection. 2: DNA/RNA extraction. The figure illustrates the gene recombination and transcription of T-cell receptors (TCRs) and B-cell receptors (BCRs). The V, D, and J gene segments of TCRs and BCRs undergo somatic rearrangement and gene insertion/deletion before transcription to generate highly variable CDR3 regions, which are then translated as TCRs and immunoglobulins. 3: Library construction by next-generation sequencing methods are used to complete the library preparation and amplification. 4: Data sequencing. 5: Data analysis. BCR: B-cell receptor; CDR3: Complementary determining region 3; TCR: T-cell receptor.

[37].

CHB patients who develop CSHB have more than 50% mortality, and the rate is related to significant increases in the levels of CD8⁺ and nonspecific T cells[38,39]. Analysis of TCR Vβ diversity in peripheral CD4⁺ and CD8⁺ T lymphocytes obtained from 18 patients with CSHB found that CD8⁺ T cells play a major role in the pathogenesis of CSHB[40]. CDR3 spectratype analysis showed predominant expression of TCR Vβ5, Vβ7, Vβ9, Vβ12, and Vβ18 families in the CD8⁺ T cell subsets of CSHB patients. In addition, JB1S1 and JB2S7 region genes were present at a high frequency. Furthermore, three conserved amino acid motifs were identified, including GSF, LF and GS, which may be involved in binding to HBV-specific antigens[40]. In contrast, TCR Vβ7 and Vβ11 were more frequently expressed in the PBMCs and CD8⁺ subsets of CSHB patients, possibly because of differences in the human leukocyte antigen (HLA) types and HBV genotype variants. Interestingly, the two CDR3 amino acid sequences had conserved BV11, AGEL or VYNEQ and BV7, QDSVTITGAQ motifs, and the CSHB patients who expressed the “AGEL” TCRBV11 CDR3 amino acid sequence had better short-term responses than patients expressing the “VYNEQ” TCRBV11 CDR3 sequence[41]. Immunostaining of liver biopsies from untreated CHB patients found the portal-periportal CD4⁺ and intralobular CD8⁺ cell frequencies were increased in severe hepatitis, which indicated that the CD4⁺ T cells were also active in the liver micro-immune environment[42].

CHB can progress to HBV-related HBV-ACLF, which is the most common type of liver failure. It is characterized by rapid deterioration of liver function, coagulopathy, and subsequent multiple organ failure with a 28-d mortality in the Asia-Pacific and African regions[43,44]. Recent studies indicated that patients with HBV-ACLF had more IL-17-producing CD8⁺ T (Tc17) cells than patients with CHB, a decrease in CD4⁺ and CD8⁺ T cells, or an increase in regulatory T cells (Tregs) in HBV-ACLF patients [45-47]. Shen *et al*[48] studied the dynamic changes of TCR repertoires in patients with HBV-ACLF and demonstrated that there was a significant decrease in the diversity of CD8 T-cell repertoire that was positively correlated with a reduction of the Model for End-Stage Liver Disease score. CD8 TCRβ repertoire diversity may be a potential predictive marker of disease outcome[48]. Yan *et al*[49] analyzed BCR heavy chain CDR3 sequences from patients with HBV-ACLF and control subjects and found that clonal expansion was more extensive in the ACLF patients and the distribution ratios of the V, D, J and VJ combinations revealed differential expression, with six upregulated genes and 19 downregulated genes in the ACLF patients. ACLF-specific BCR CDR3 sequences hold future therapeutic promise for HBVACLF[49].

Table 2 Specific TRB family and clinical significance

TRB family	Clinical significance
TRBV β 2	Development and treatment of CHB
TRBV β 3	HBeAg seroconversion
TRBV β 5	Severity of CHB
TRBV β 7	Development and treatment of CHB, severity of CHB
TRBV β 9	Severity of CHB
TRBV β 11	HBeAg seroconversion, severity of CHB
TRBV β 12	Development and treatment of CHB, HBeAg seroconversion, severity of CHB
TRBV β 14	HBeAg seroconversion
TRBV β 18	Severity of CHB
TRBV β 20	HBeAg seroconversion
TRBV β 24	HBeAg seroconversion
TRBV β 28	Development and treatment of CHB

CHB: Chronic hepatitis B; HBeAg: Hepatitis B e antigen.

HBV is the most common cause of HCC, with an estimated prevalence of 44%-55% of HCC cases worldwide[50]. The mechanism underlying HBV-related HCC and other HBV-related liver cancers is not clear. Some studies have shown that the HBV x gene promotes cell cycle progression, inactivates negative growth regulators, and inhibits the expression of the p53 tumor-suppressor gene[51]. The adaptive immune system also plays an important role in carcinogenesis. An investigation of TRB V usage in HBV-associated HCC found that the T-cell repertoires of HCC, intrahepatic cholangiocarcinoma, and mixed hepatocellular and cholangiocellular carcinoma tumors and adjacent tissues were significantly different ($P < 0.01$). The highly expanded clone ratio in blood samples from liver cancer patients differed significantly from those in the blood of healthy adults and hepatitis patients. The results suggest that comparison of the T-cell repertoires of tissue and blood could be used to distinguish liver cancer patients from healthy adults and from hepatitis patients[52].

APPLICATION OF IMMUNE REPERTOIRE ANALYSIS IN HBV THERAPY

Current treatment of CHB is limited to nucleos(t)ide analogs, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and others, which block DNA synthesis; and interferon- α , which directly suppresses viral RNA and protein production in infected cells and inhibits HBV DNA replication. It also activates NK cells and T cells that target HBV-infected cells[2]. Studies that evaluated HBV treatment found differences in the antiviral effect that were associated with the adaptive immune response. Yan *et al*[53] reported that telbivudine reduced HBV DNA levels and downregulated the proportion of circulating Tregs. A reduction in the Treg proportion was observed in CHB patients during TDF treatment[54].

A clinical trial including 12 patients with HBeAg seroconversion and 20 without seroconversion who were treated with 300 mg TDF daily for 96 wk found a T-cell receptor beta-chain variable (TCRBV) family that was associated with HBV DNA levels in the seroconversion group[55]. Six TCRBV families (BV3, BV11, BV12, BV14, BV20, and BV24) were more prevalent than the other TCRBVs in the seroconversion group. BV12, BV15, and BV22 were predominant in the patients who had not seroconverted. In addition to the Treg frequency and alanine aminotransferase (ALT) level, the Treg profile and TRBVs were associated with HBeAg seroconversion and may be potential predictors of HBeAg seroconversion and treatment outcome in CHB patients [55,56]. A recent TCR repertoire study by Lian *et al*[57] in 20 CHB patients undergoing 1-year ETV treatment found that the diversity of TCR β repertoires was decreased in the 10 HBeAg- seroconverted patients but increased in the 10 patients without HBeAg seroconversion. The number of unique TCR β clonotypes was positively correlated with the ALT or HBV DNA level in seroconverted patients, which indicated that the

TCR repertoire along with ALT or HBV DNA level may be a biomarker to predict HBeAg seroconversion during and after antiviral treatment[57]. The TRB family specific to HBV infection and its clinical significance are shown in Table 2.

APPLICATION OF IMMUNE REPERTOIRE ANALYSIS IN HBV VACCINATION

The immune repertoire plays an important role in HBV vaccine response. The HBV vaccine consists of recombinant HBsAg, an aluminum hydroxide adjuvant, and/or a virus-like particle that stimulates T-helper (Th2) cells to produce IL-4 to promote the production of anti-HBsAg antibodies[58]. The human TCR repertoire response to HBsAg is oligoclonal, involves multiple TCRBV families, and has individual specificity [59]. Analysis of the TCR-VA and -VB repertoire in CD8⁺ T cells from individuals immunized with recombinant HBsAg detected monoclonal TCR transcripts exclusively in CD8⁺, but not in CD4⁺ T cells[60]. TCR β chain CDR3 repertoire diversity increased, and the BCR IgG H chain CDR3 repertoire diversity decreased, indicating that diversity changes may be associated with a better response to the HBV vaccine [61]. An investigation of the BCR repertoire by Galson *et al*[62,63] found that vaccine-specific BCR sequence clusters expanded after each of three sequential vaccine doses. Additionally, many vaccine-specific BCR clusters appeared to largely derive from previously activated cross-reactive B cells that had low affinity for the vaccine antigen, and subsequent doses were required to yield higher affinity B cells[62,63]. Analysis of the IgG and IgM heavy chain CDR3 repertoire before and after immunization with recombinant HBV vaccine, found the diversity of IgG heavy chain CDR3 repertoires was 1/6 of IgM on average[64]. Moreover, the mechanism of high frequency CDR3 generation was associated with the maturation of IgG affinity[64].

About 5% to 10% of healthy adults fail to produce protective levels of anti-hepatitis B surface antibodies after vaccination with recombinant anti-HBsAg vaccines[58,65]. In “nonresponders,” the mechanisms that contribute to the lack of humoral immune response to HBsAg include defective in Th1- and Th2-specific responses, dysfunction of antigen-presenting cells, immunologic tolerance, and too few HBsAg-specific B cells and T cells[66-68]. Study of the immune repertoire could provide a new perspective to overcome obstacles by understanding the adaptive immune profile to HBV vaccination. Differences in the BV5S2-3 gene family in CD4⁺ T cells and several TCR BV genes, such as BV12 in the CD4⁺ population and BV24 in the CD8⁺ population, may explain the unresponsiveness to recombinant HBsAg vaccine[69].

CONCLUSION

IRS has demonstrated its potential in advancing our understanding of the progression of HBV infection, antiviral treatment, and vaccination. Ongoing study of immune repertoires in the field of HBV infection, overcoming technical problems, and increased sharing of sequencing data, the reporting of interesting clinical discoveries will increase.

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