

Chemokines and Their Receptors in Hepatitis B Virus Infection: A Comprehensive Review

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Abstract

Chemokines, a group of small cytokines, play a central role in the pathogenesis of viral hepatitis by regulating the migration, proliferation, and activation of lymphocytes. These chemotactic factors of immune cells are directly involved in various cellular biological activities, including cell adhesion, angiogenesis, and diffusion. The aberrant expression of lymphocyte chemokines and their receptors is closely related to the biological behavior of host immune cells as well as the specific and non-specific immune responses to viral infections and may influence the prognosis of viral diseases. The intricate interplay between chemokines, their receptors and lymphocyte migration in the context of liver immunity needs further investigation. In this article, we provide an overview of the role and associated mechanisms of chemokines and their receptors in hepatitis B virus (HBV) infection and pathogenesis and highlight their potential therapeutic implications.

Keywords: HBV infection, Chemokines, Chemokine receptor, Pathogenesis

Introduction

Infection with the hepatitis B virus (HBV) is a global health problem. Approximately 2 billion people in the world are infected with HBV, including 350 to 400 million people with chronic hepatitis B [1]. In general, the prognosis of HBV infection depends on age at the time of HBV infection, virus type and host immunity. Studies have shown that adults infected with HBV usually develop an acute infection. In about 95% of affected individuals, the acute infection is self-limiting and lifelong immunity persists after recovery [2]. However, newborns, infants and children (usually under 5 years of age) infected with HBV are prone to chronic HBV infection and could develop lifelong disease if they do not receive effective treatment, which can easily lead to chronic hepatitis B (CHB), cirrhosis or even hepatocellular carcinoma (HCC) [3,4]. The occurrence and development of HCC are closely related to the

host immune microenvironment.

Chemokines and their receptors play crucial roles in the immune response by activating inflammatory cells, aiding their development, and directing their movement to inflammation sites. They also contribute to angiogenesis, tissue repair, tumor growth, and metastasis [5]. In recent years, some studies showed that chemokines are closely related to the occurrence, development, treatment and prognosis of viral hepatitis B [6]. In this view, we performed a systematic search in databases such as PubMed, Scopus, and Web of Science using keywords such as 'chemokines', 'receptors', 'hepatitis B', and 'viral infection'. Studies published in the last ten years were considered to ensure relevance and accuracy. We focused on finding high quality articles that include both primary research and previous reviews. We critically evaluated the methodology of these studies by assessing the study

design, sample size, statistical analyses, and potential biases. We have considered the reproducibility of the results and whether the conclusions are supported by the data. Finally, we have summarized and synthesized the results by pointing out contradictory results and research gaps.

Overview of HBV and Chemokine

Hepatitis B virus

HBV is a non-cellular, small DNA double-stranded virus. HBV infection leads to a series of host immune responses, and the different stages of immune response are associated with the different stages of chronic HBV infection [7]. After HBV enters the body, the virus is taken up by antigen-presenting cells (APCs) and processed into immunological polypeptides, which are combined with MHC (MHC II, I) and transported to the surface of APCs, where they are recognized by the T cell receptor (TCR) of CD4+T cells or CD8+T cells [8, 9]. The TCR, the polypeptide and its APC (MHC) form a complex, followed by a series of cascade reactions that regulate the proliferation and differentiation of effector T cells, which then exert cellular and humoral immunity against HBV [10].

In the process of the immune system against HBV, specific lymphocytes interact with viral antigens, numerous cytokines are released, leading to an exaggerated immune response and liver cell damage [11]. If the immune system is healthy and can completely eliminate the virus, the infection is self-limiting; however, if the immune system is immature or the body has low immunity, which means that the host cannot completely eliminate the virus in time, the HBV infection is persistent [12]. As for the mechanism, the extent and outcome of chronic HBV infection is related to the migration of lymphocytes into

the liver tissue. The migration process is controlled by many factors, with the interaction between chemokines and their receptors being one of the most important factors [13].

Chemokines

Since 1986, a class of cytokines with a chemotactic effect on white blood cells has been discovered, which are mainly produced by immune cells. At the 3rd International Symposium on Chemotactic Factors in 1992, it was defined as a chemoattractant (chemotactic) cytokine and translated as chemotactic factor. There are more than 50 known chemokines, which can be divided into four subfamilies based on the arrangement of the N-terminal cysteine residues (Cys), namely CXC, CC, C, and CX3C [14]. In general, the common characteristics of chemokines are: 1) Low molecular weight, usually between 8~10 kD; 2) Derived from the same ancestral gene; the proteins exhibit homology in their primary structure, and most chemokines contain four conserved Cys. The Cys at positions 1 and 3 and the Cys at positions 2 and 4 form two pairs of disulfide bonds, which are essential for their function; 3) Different chemokines have similar spatial structures and good N-terminal folding ability, with 3 β-folds, 1 α-helix at the C-terminus; 4) Their corresponding receptor belongs to the G-protein-coupled receptors [15]. In addition, the basic functions of chemokines include 1) Chemotaxis; 2) Regulation of integrin expression and white blood cell activation; 3) Promotion of cell degranulation and release of bioactive substances; 4) Growth factor activity promotes cell proliferation; 5) Regulation of angiogenesis. In addition, the abbreviations, characteristic parameters and functions of the chemokines discussed in the review are listed in **Tables 1 and 2**.

Table 1. Abbreviations, full names, and aliases of chemokines.		
Abbreviation	Full Name	Alias
CCL2	Chemokine (C-C Motif) Ligand 2	Monocyte chemoattractant protein-1 (MCP-1)
CCL3	Chemokine (C-C Motif) Ligand 3	Macrophage inflammatory protein-1 alpha (MIP-1 alpha)
CCL4	Chemokine (C-C Motif) Ligand 4	Macrophage inflammatory protein-1 beta (MIP-1 beta)
CCL5	Chemokine (C-C Motif) Ligand 5	Regulated on activation, normal T cell expressed and secreted (RANTES)
CCL20	Chemokine (C-C Motif) Ligand 20	Lymphotactin-2 or macrophage inflammatory protein-3 alpha (MIP-3 alpha)
CXCL8	Chemokine (C-X-C Motif) Ligand 8	Interleukin-8 (IL-8)
CXCL9	Chemokine (C-X-C Motif) Ligand 9	Monokine induced by gamma interferon (MIG) or Interferon-gamma-inducible protein 9 (IP-9)
CXCL10	Chemokine (C-X-C Motif) Ligand 10	Interferon-gamma-inducible protein 10 (IP-10)
CXCL12	Chemokine (C-X-C Motif) Ligand 12	Stromal cell-derived factor 1 (SDF-1)
CXCL13	Chemokine (C-X-C Motif) Ligand 13	B-lymphocyte chemoattractant (BLC)
CXCL16	Chemokine (C-X-C Motif) Ligand 16	Scavenger receptor-C-type lectin (SR-PSOX)
CX3CL1	Chemokine (C-X3-C Motif) Ligand 1	Fractalkine

Table 2. Characteristic parameters and functions of chemokines.					
Chemokine	Size (KDa)	Family Category	Expression Location	Cellular Sources	Function (Recruitment/ attract)
CCL2	8	CC	PBMCs, endothelial cells, Mφ	Mφ, DC, T cells	Monocytes DC
CCL3	8	CC	Lymphoid tissues, sites of inflammation	Monocytes, T cells, mast cells, NK cells	Monocytes, lymphocytes, NK cells
CCL4	8	CC	Lymphoid tissues, sites of inflammation	Monocytes, T cells, mast cells, NK cells	Monocytes, lymphocytes, NK cells
CCL5	9	CC	Lymph nodes, spleen, lung	DC, Mφ, endothelial cells	Monocytes, basophils, eosinophils
CCL20	12	CC	Skin, lung, spleen	Keratinocytes, DC, Mφ	DC
CXCL8	10	CXC	Skin, lung, colon	Neutrophils, Mφ, DC	Neutrophils
CXCL9	11.5	CXC	Endothelial cells, fibroblasts, epithelial cells	Monocytes, endothelial cells, fibroblasts	Activated T cells, NK cells; promotes Th1 responses
CXCL10	10	CXC	Lymph nodes, spleen, bone marrow	Monocytes, Mφ, DC	Neutrophils, DC
CXCL12	12	CXC	Lung, skin, gastrointestinal tract	Epithelial cells, Mφ, DC	Neutrophils, DC
CXCL13	10	CXC	Skin, lung, lymph nodes	Keratinocytes, DC, endothelial cells	Neutrophils
CXCL16	10	CXC	Skin, lung, gastrointestinal tract	Keratinocytes, DC, Mφ	Neutrophils, DC
CX3CL1	12.5	CX3C	Various tissues, including endothelial cells	Endothelial cells, neurons, epithelial cells	T cells, monocytes, NK cells; adhesion molecule for leukocytes
The sizes of chemokines are approximate and may vary slightly depending on the source. DC: Dendritic Cell; Mφ: Macrophage					

Chemokine receptors

Chemokines mediate the migration of white blood cells by binding to their respective receptors on the target cells [16]. Chemokine receptors are transmembrane receptors that mediate the function of chemokines and are typically expressed on cell membranes such as immune cells, epithelial cells, smooth muscle cells and fibroblasts. Chemokine receptors belong to the superfamily of G protein-coupled receptors (GPCRs), which consist of seven transmembrane G protein-coupled receptors rich in seven G-helix transmembrane regions with hydrophobic amino acids that transmit signals via heterotrimeric G proteins. Depending on the type of chemokines, chemokine receptors are divided into four categories: CXCR, CCR, CR and CX3CR. Chemokines bind to receptors and activate G proteins. Through a series of signal transductions, chemotactic target cells migrate to sites of inflammation and aggregate, activate and release various inflammatory mediators that play an important role in immune response processes such as the body's defense

against infection [17]. There is no one-to-one correspondence between chemokines and receptors.

Chemokines and Their Receptors in Hepatitis B

Research has confirmed that a viral infection and the expression of chemokines and their receptors in the host cells interact and are mutually dependent [18]. Viral infection can trigger the expression of chemokines and their receptors in the host cell, and the strength of this expression can also influence the host's immune response to the virus. At the same time, certain viruses can themselves encode chemokines or chemokine receptor-like molecules and thus disrupt the network function of chemokines and their receptors [19], which has an impact on the prognosis of the disease. In the elimination of HBV in the body, the cellular immune response, in particular the virus-specific T-killer lymphocytes (CTL) as the most important effector cells, plays a crucial role in the body's anti-HBV immune response. To eliminate virus, CTL must first reach the site of viral infection to exert their function. Studies

have shown that chemokines of the CXC subfamily are mainly involved in the chemotaxis and activation of inflammatory cells in acute inflammatory reactions, while chemokines of the CC subfamily mainly mediate the chemotaxis and activation of monocytes and lymphocytes in chronic inflammatory processes [20].

CCL2

Monocyte chemoattractant protein-1 (MCP-1), also known as CCL2, was discovered by Valente in 1988 and is the first CC-type chemokine to be discovered [21]. It consists of 76 amino acid residues and the expressed gene contains 3 exons and 2 introns. MCP-1 is produced by various cells such as endothelial cells, epithelial cells, fibroblasts, smooth muscle cells, glomerular mesangial cells, stellate cells, monocytes, and microglia. The main target cells are monocytes and macrophages, and it also has some chemotactic effect on activated NK cells and memory T cells. MCP-1 can activate basophils and cause them to release drugs such as histamine [22]. It is associated with the activation of monocytes and lymphocytes in inflammatory responses and can induce T cells to adhere to fibronectin and extracellular matrix. Han *et al.* constructed a HepG2-HBx cell line stably expressing HBx and found that HBx selectively downregulated the expression of the human liver cell line MCP-1. The study by Shen *et al.* [23] showed that the concentration of MCP-1 in the serum of CHB patients decreased and there was a negative correlation between MCP-1 concentration and serum HBV DNA load. Therefore, the decreased expression of MCP-1 may impair the activation and chemotaxis of monocytes and macrophages, thereby reducing the clearance efficiency of host immune cells against the virus to some extent, which may be a mechanism by which HBV can evade the host immune response.

CCL3

CCL3 or macrophage inflammatory protein-1 α (MIP-1 α) is an important chemokine in the immune response to HBV infection and is used to attract immune cells such as monocytes, T cells and basophils to the site of infection [24]. These cells, once activated, play a crucial role in fighting the virus; monocytes develop into macrophages to engulf the virus, T cells target and eliminate infected cells, and basophils enhance the immune response by releasing histamine and other mediators. As an important molecular messenger, CCL3 facilitates the recruitment and activation of these immune components to effectively combat HBV infection [25]. However, an imbalance in the expression or activity of CCL3 can lead to persistent HBV infection and possibly chronic liver disease, highlighting its importance in HBV pathogenesis and its potential as a target for therapeutic intervention.

CCL4

CCL4, also known as macrophage inflammatory protein-1 β

(MIP-1 β), is a critical pro-inflammatory chemokine that plays an important role in the immune response to HBV infection [26]. This chemokine is primarily responsible for attracting and recruiting various immune cells, such as monocytes, T cells and basophils, to the sites of inflammation. In this way, CCL4 contributes to an effective immune response against HBV aimed at controlling and eliminating the infection. However, excessive or prolonged production of CCL4 can contribute to chronic inflammation and tissue damage, which can lead to the development of severe liver diseases such as cirrhosis and hepatocellular carcinoma [27]. Therefore, understanding the regulation and function of CCL4 in HBV infection is critical for the development of new therapeutic strategies to manage and treat this global health burden.

CCL5

Regulated upon activation, normal T cell expressed and secreted (RANTES) is a chemotactic factor of the CC subfamily, also known as CCL5, which is secreted by normal T cells [28]. RANTES can not only act chemotactically and activate inflammatory cells during the inflammatory process, but also interact with inflammatory factors to prolong and exacerbate the inflammatory response. CCL5 was discovered in 1988 by Schall *et al.* [29] while searching for new genes for T cell expression. RANTES can be produced by NK cells, T cells, liver cells, fibroblasts, and platelets and is regulated by IL-1 IFN- γ , and TNF- α , its receptors are mainly CCR1, CCR3, and CCR5. Duan *et al.* [30] found that the polymorphism of the single nucleotide gene RANTES has no effect on chronic HBV infection or the outcome of interferon-alpha treatment in patients with positive HBV "e" antigen (HBeAg+), but the increased expression of RANTES in the plasma of patients with CHB suggests an association with the chronicity of HBV infection. Wei *et al.* [31] found that the expression of RANTES in liver tissue of CHB patients was higher than that in the healthy group, and the expression of RANTES in liver cells in areas with severe inflammatory responses was also significantly increased; with increasing clinical grading and grading of liver inflammation in CHB patients, the expression intensity of RANTES in liver tissue gradually increases, suggesting that RANTES plays an important role in the development of liver inflammation in CHB patients.

CCL20

Recombinant mouse macrophage inflammatory protein-3 α (MIP-3 α , CCL20, liver and activation-regulated chemokine, LARC) was discovered in 1997 by the Japanese scientists [32]. CCL20 is expressed in liver tissue, skin keratinocytes, and intestinal epithelial cells, among others, and its main target cells are activated T lymphocytes. Shao *et al.* [33] developed liver cell models with different infection states of HBV using *in vitro* gene transfection technology. Internal control RT-PCR was used to detect CCL20, and it was found that the expression of CCL20 increased sequentially in liver cells infected with HBV,

uninfected liver cells, and liver cells continuously infected with HBV. At the same HBV infection status, there was no significant correlation between the expression level of CCL20 and HBV infection time, cell culture time, and viral load, suggesting that different HBV infection states affect the expression of CCL20 [34]. After comparing the expression of CCL20 in the control group and in liver tissue in CHB, it was found that CCL20 is constitutively expressed in liver tissue. In chronic persistent HBV infection, the expression of CCL20 was downregulated and correlated with the histologic score of the liver. By using gene recombination technology to construct eukaryotic expression vectors of the chemokine CCL20 and surface antigen (HBsAg) and injecting them into normal C57BL/6 mice, a high titer of anti-HBs antibodies was detected in 100% of mice at weeks 4 and 6 and persisted for up to 10 weeks, suggesting that CCL20 enhances the cellular immune response to HBsAg [35]. Abnormal expression of CCL20 reduces T lymphocyte chemotaxis, impairs viral clearance implying it is involved in the mechanism of HBV infection moderation. The enhanced effect of CCL20 on the immune response to HBsAg could provide a basis for targeted treatment of hepatitis B.

CXCL8

Interleukin-8 (IL-8) was purified in 1987 by Yoshimura *et al.* [36] from the supernatant of human peripheral blood monocytes stimulated by bacterial lipopolysaccharide (LPS) and belongs to the ELR CXC chemokines. Its coding gene is located between 4q12 and q21 and encodes a precursor protein of 99 amino acids. Due to differences in N-terminal cleavage, IL-8 precursor protein generates multiple peptide molecules, with peptides of 72 and 78 amino acid residues being most abundant. IL-8 is a multifunctional factor with no species-specific biological function. In recent years, IL-8 has been found to have a chemotactic effect on neutrophils, T cells, and monocytes [37]. It can cause degranulation of white blood cells and release of elastase, be involved in the regulation of immune response, metabolic response and acute inflammatory phase, and enhance the body's ability to defend against infection [38]. Several immune cells and liver cells infected with HBV can secrete IL-8, LPS, IL-1, and TNF- α and stimulate their extensive expression. Previous studies [39] have shown that the expression of IL-8 increases in the serum of chronically HBV-infected individuals and increases with disease exacerbation. Liu *et al.* [40] investigated serum IL-8 levels in patients with hepatitis B and liver cirrhosis. The results showed that serum IL-8 levels were higher in patients with liver cirrhosis than in healthy individuals and increased with increasing Child-Pugh grading, suggesting that IL-8 plays an important role in the progression of liver cirrhosis. Alqaderi *et al.* [41] found that serum IL-8 concentrations were higher in patients with severe hepatitis B than in healthy individuals and patients with CHB. This suggests that serum IL-8 concentration is a clinical index for the assessment of the severity and prognosis of severe hepatitis B.

CXCL9

CXCL9, also known as monokine induced by interferon- γ (MIG), is a chemokine that plays a crucial role in controlling the immune response to HBV infection. Its main function is to attract T cells, particularly Th1 cells, to sites of inflammation [42]. These Th1 cells are crucial for a robust antiviral response against HBV. CXCL9 achieves this recruitment by binding to its receptor CXCR3, which is expressed on the surface of Th1 cells. Upon binding, CXCL9 triggers a signaling cascade that directs these immune cells towards the infected liver where they can effectively fight the virus. The presence of elevated levels of CXCL9 in the blood of HBV patients is often indicative of active inflammation and serves as a potential biomarker for disease severity [43]. Understanding the role of CXCL9 in HBV infection could pave the way for new therapeutic strategies aimed at modulating the immune response and improving treatment outcomes.

CXCL10

The human IP-10 gene was isolated by Luster in 1985 during treatment of lymphoma cells (U937) with recombinant γ -interferon (IFN- γ) [44]. The IP-10 gene is located on chromosome 4q21 and contains 3 introns and 4 exons consisting of 98 amino acid (Aa) residues. The primary sequence contains four conserved cysteine residues, and its N terminus does not contain an ELR sequence that does not belong to the ELR CXC family. The primary translation product of the IP-10 gene is a protein with 2 internal disulfide bonds (with MW 12000 Da), which is predicted to yield a secreted peptide with 4 conserved cysteine residues at the N-terminus (with MW 10000 Da) by signal peptidase cleavage.

IP-10 exerts its biological function by binding to its specific receptor CXCR3 [45]. Simply, the CXCR3 gene is located in xP13, has a total cDNA length of 1104 bps, and encodes 368 amino acids. It is a G protein-coupled transmembrane receptor with seven subunits. The induction of IP-10 depends mainly on the carboxyl-terminal region of CXCR3. Colvin *et al.* [14] suggest that IP-10 induced activation of the CXCR3 receptor involves phosphorylation of the carboxyl-terminal serine and threonine of CXCR3, uncoupling of the β -inhibitor protein in the G protein, and internalization of the CXCR3 receptor. IP-10 is a multifunctional molecule that can exert effective biological functions, including promoting chemotactic regulation of CXCR3+ cells, inducing cell apoptosis, regulating cell growth and proliferation, and inhibiting angiogenesis [46].

Viral infection can stimulate Th1 cells to secrete IFN- γ , which may increase the expression of CXCL10 in liver sinusoidal endothelial cells. Therefore, the highly expressed CXCL10 in the liver tissue of patients with CHB can migrate into the liver tissue through chemotaxis and activation of monocytes and lymphocytes expressing its receptor CXCR3 and play the role of supporting CTL and activating other immune cells in the

infected area. At the same time, the activated cells secrete more chemokines to further promote the aggregation of lymphocytes in the liver [47]. Studies have shown that serum level of IP-10 is a promising predictor of HBsAg decline in naive HBeAg-negative chronic hepatitis B patients treated with entecavir for four years [48].

In recent years, an increasing number of studies have shown that IP-10 is associated with the response to CHB treatment. Our previous study suggests that the dynamic change of CXCL10 is closely related to the prognosis of CHB patients under antiviral treatment [49]. Papathodoridis *et al.* [50] found that entecavir can reduce serum hepatitis B surface antigen (HBsAg) levels in patients with hepatitis B e-antigen (HBeAg) negative CHB, and serum IP-10 levels have a predictive effect on the degree of HBsAg decline. The baseline IP-10 level is positively correlated with ALT level and negatively correlated with HBsAg level. Furthermore, our studies show that CXCL10 and its receptor are able to predict HBeAg seroconversion during treatment with tenofovir (TDF) in CHB patients [51].

CXCL12

Stromal cell-derived factor-1 (SDF-1), also known as CXCL12 or pre-B cell stimulatory factor (PBSF), was isolated in 1994 by Nagasawa *et al.* [52] from the culture supernatant of the stromal cell line PA6 from the bone marrow of mice. SDF-1 is crucial for the growth and differentiation of lymphocytes, especially lymphoid progenitor cells. In contrast to other chemokines, SDF-1 is continuously secreted by stromal cells and is not induced by inflammatory factors. It interacts exclusively with the CXCR4 receptor and thus forms the SDF-1/CXCR4 axis, which is crucial for the development and maturation of B cells and is necessary for the formation of pre-B cells in the bone marrow [53].

In addition, SDF-1 is secreted by bile duct epithelial cells and can mediate the aggregation of bone marrow-derived liver stem cells, promoting their differentiation into hepatocytes and bile duct cells. This mechanism helps in the repair and regeneration of liver tissue. [54]. Wald *et al.* [55] discovered that chronic hepatitis C and B lead to a redistribution of CXCL12 in the liver, with increased expression in neovascular endothelial and inflammatory cells, highlighting its role in the recruitment and maintenance of immune cells in liver tissue. Moreover, binding of CXCL12 to CXCR4 on T cells influences their tumor infiltration. T cells with higher antigen affinity and lower CXCR4 expression are less likely to exit the tumor, a finding that has significant implications for tumor immunotherapy [56].

CXCL13

CXCL13 belongs to the CXC family of chemokines, is encoded by the CXCL13 gene on chromosome 4 and is secreted by stromal cells in the B-cell region of the secondary lymphoid organ (SLO) [57], which is why it is also referred to as a B-cell

chemotactic. Studies in mouse models have shown that CXCL13 is mainly derived from macrophages and is expressed in an age-dependent manner in liver macrophages, which are involved in the development of lymphoid structures and the transport of B cells, thereby triggering the body's immune response [58]. In the human body, CXCL13 is mainly produced by follicular T helper cells (Tfh) and peripheral T helper cells (Tph). Tfh are a specialized subset of CD4+T cells that reside in lymphoid follicles and represent an important cell subset that supports B cells in their function [59]. Tfh express CXCR5, PD-1, BCL-6, etc. They can promote B cell differentiation and maturation by producing IL-21 and CXCL13 and regulate germinal center (GC) formation in SLO. Similar to Tfh, Tph is a new group of CD4+T cell subpopulations discovered in recent years that can promote the recruitment of CXCR5+ lymphocytes and the formation of lymphoid follicles by secreting CXCL13 [60]. In contrast to Tfh, Tph expresses neither CXCR5 nor BCL-6.

CXCL16

CXCL16, a new chemokine discovered by Matloubian *et al.* [61], belongs to the CXC family and contains a similar transmembrane domain to CX3CL1. CXCR6 is currently the only known receptor for CXCL16. The human CXCL16 gene is located on chromosome 17P13 and does not contain an ELR amino acid sequence. CXCL16 is produced by spleen cells, cells in lymph nodes (including dendritic cells, which contribute to triggering immune responses) and red spleen cells. CXCR6 is mainly expressed in memory T cells, endothelial lymphocytes, B cells, NK cells, T cells, dendritic cells, CD4+ Th1 and activated CD8+T cells. CXCL16 is expressed in liver parenchymal cells, bile duct cells, sinusoidal endothelial cells and perihepatic cells in normal liver tissue [62]. CXCL16 is significantly upregulated in tissues with liver injury, which may promote liver infiltration by chemotactic and adherent recruitment of lymphocytes, favor the destruction of bile duct and liver cells, and be involved in liver tissue injury [62]. Ajmera *et al.* [63] found that serum CXCL16 levels were significantly higher in the acute and chronic hepatitis B group than in the normal control group. The CXCL16 concentration is related to the condition of hepatitis B and worsens as the disease worsens.

CX3CL1

CX3CL1, also known as fractalkine, is a unique chemokine that plays a crucial role in the immune system by attracting T cells and natural killer (NK) cells. It is particularly important for the recruitment of these immune cells to sites of inflammation, such as hepatitis B virus (HBV) infection [64]. CX3CL1 acts via its receptor CX3CR1 and thus facilitates a targeted immune response against infected cells. This chemokine not only helps direct the movement of immune cells to the site of infection, but also supports their adherence and survival, which is critical for an effective immune response [65]. Its ability to mediate both cell migration and cell adhesion makes it an

important player in the control and resolution of HBV-related inflammation, potentially impacting disease progression by improving the immune system's ability to fight the virus.

Summary and Outlook

In summary, chemokines bind to their receptors after HBV infection to target specific inflammatory and immune cells at the site of the lesion and participate in the inflammatory response [66]. However, different HBV infection stages, states of host immune function and the expression of chemokines and their receptors in host cells interact with each other and lead to different disease courses, and the changes in

the expression of chemokines at different disease stages are also different (Table 3). Therefore, there are still many urgent questions about the mechanism of action of chemokines and their receptors at different stages of HBV infection, such as the specific role of chemokines in the body's immune response after HBV infection; the specific mechanisms involved in the process of chronic and severe HBV infection; the regulatory mechanisms between different chemokines and their receptors; the effects of chemokines on antiviral therapy. In addition, other chemokines and their receptors [67] are also involved and play a role in the pathogenesis of persistent HBV infection.

Table 3. Changes in the expression of chemokines at different stages of the disease.				
Chemokine	Disease	Early Stage	Intermediate Stage	Late Stage
CCL2	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CCL3	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CCL4	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CCL5	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CCL20	Psoriasis	↑	↑	↑
	Inflammatory Bowel Disease	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CXCL8	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CXCL9	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CXCL10	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CXCL12	Cancer (various types)	↑ (PTG&M)	↑	↑

CXCL13	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CXCL16	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
CX3CL1	RA	↑	↑	↑
	MS	↑	↑	↑
	Cancer (various types)	↑ (PTG&M)	↑	↑
Note that the changes may vary depending on the disease and the study. For example, while many chemokines in cancer promote tumor growth and metastasis, some may also have an antitumor effect. Therefore, the specific context and disease stage should be considered when interpreting chemokine changes.				
↑: Increased; MS: Multiple Sclerosis; PTG&M: Promotes Tumor Growth and Metastasis; RA: Rheumatoid Arthritis				

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Jiezuan Yang and Dan Cao contributed to the study design and the writing of the original draft. Ruiqi Tang and Xuefen Li contributed to the study coordination, technical issues and revision of the manuscript.

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