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REVIEW



Role of chemokine systems in cancer and inflammatory diseases

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Abstract

Chemokines are a large family of small secreted proteins that have fundamental roles in organ development, normal physiology, and immune responses upon binding to their corresponding receptors. The primary functions of chemokines are to coordinate and recruit immune cells to and from tissues and to participate in regulating interactions between immune cells. In addition to the generally recognized antimicrobial immunity, the chemokine/chemokine receptor axis also exerts a tumorigenic function in many different cancer models and is involved in the formation of immunosuppressive and protective tumor microenvironment (TME), making them potential prognostic markers for various hematologic and solid tumors. In fact, apart from its vital role in tumors, almost all inflammatory diseases involve chemokines and their receptors in one way or another. Modulating the expression of chemokines and/or their corresponding receptors on tumor cells or immune cells provides the basis for the exploitation of new drugs for clinical evaluation in the treatment of related diseases. Here, we summarize recent advances of chemokine systems in protumor and antitumor immune responses and discuss the prevailing understanding of how the chemokine system operates in inflammatory diseases. In this review, we also emphatically highlight the complexity of the chemokine system and explore its potential to guide the treatment of cancer and inflammatory diseases.

KEYWORDS

cancer progression, chemokine, chemokine receptor, inflammatory diseases, tumor microenvironment (TME)

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1 | INTRODUCTION

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Chemokines (chemotactic cytokines or chemoattractant cytokines) are a complicated family of small secreted proteins that, when bound to the corresponding cell surface receptors, have a fundamental role in the development of human organs, physiological function, and homeostasis of the immune system. All chemokines are 8-12 kDa peptides that modulate cellular chemotactic migration, adhesion, localization, and cell-cell interactions through binding to the so-called classical seven transmembrane receptors, that is, G protein-coupled receptors (GPCRs).^{1,2} Chemokines can also bind to atypical chemokine receptors (ACKRs) with high affinity, which are non-G protein-coupled seven-transmembrane receptors that do not induce directional cell migration. Indeed, ACKRs mainly activate β -arrestin-dependent pathways that regulate the bioavailability of chemokines and modulate the expression of other typical chemokine receptors or downstream signaling pathways, thus playing a role in immune responses.³ Chemokines possess a spectrum of characteristics and functions. Some chemokines are secreted without stimulation, which are called homeostatic chemokines and govern the chemotaxis of immune cells during immune surveillance, such as the induction of lymphocytes to lymph nodes. One function of the homeostatic chemokines is monitoring pathogen invasion by interacting with antigen-presenting cells in tissues.^{4,5} Other chemokines stimulate the formation of new blood vessels (angiogenesis), facilitate cells into tissues, and deliver specific signals for cell maturation, playing a major role in development.⁶ There are also chemokines that can be released by various cells in response to viral or bacterial infections; such chemokines can also be produced in response to noninfectious stimuli, such as inhalation of silica and the presence of urinary stones, and thus exert important functions in the inflammatory response.⁷ This group of inflammatory chemokines is released by many different types of cells and constitutes the bulk of the chemokine family. Inflammatory chemokines primarily act as chemotactic agents for leukocytes (e.g., monocytes and neutrophils), attracting leukocytes from the circulation to the site of infection or tissue damage, and activating cells to illicit an immune response or promoting wound healing.⁸ Owing to their molecular stability and targeting specificity, chemokines are thought to be critical for leukocyte infiltration and subsequent elicitation of inflammatory responses, directing the natural and adaptive immune response of the host.⁷

Given the diversity and dynamic regulation of chemokine ligand and chemokine receptor expression by tumor cells, stromal cells, and immune cells, the role of chemokines in tumor immunity is multifaceted. The tumor microenvironment (TME) is formed by cancer

cells, tissue-resident cells (like fibroblasts, endothelial cells), and infiltrating immune cells that express multiple chemokines and chemokine receptors.9-11 In TME, chemokines act on tumor cells to regulate their proliferative, invasive, and stem cell properties; and in turn, chemokines generated by tumor cells appeal to leukocyte infiltration, regulate neurogenesis and fibrogenesis, and induce vascularization, thereby affecting the microenvironment.¹² However, the role of chemokines in regulating key aspects of immune cell activation, localized recruitment, phenotypic differentiation, and function within the TME during tumorigenesis is only beginning to be discovered.¹³ To complicate matters further, the same chemokine system contributes to both protumor and antitumor immune responses. The stage of disease onset, the activation status of immune cells, and the expression of chemokine receptors on regulatory and effector target cells may all have an impact on the balance between the different functions.^{13,14} Further studies of chemokine systems in malignant tumors will not only provide a better understanding of cancer biology, but more importantly will also suggest novel therapeutic strategies for cancer immunotherapy. The regulation of the immune system by chemokines and chemokine receptors is also involved in a variety of inflammatory diseases other than tumors, such as rheumatoid arthritis (RA), multiple sclerosis (MS), asthma, type 2 diabetes, and atherosclerosis.^{15,16}

We will attempt to make a brief summary of the classification and structure of chemokines, highlighting recent advances in the function of the eight most currently reported chemokine axes in cancer progression and cancer immune response. We also summarize the latest understanding of how these chemokine systems operate in inflammatory diseases. We focus on the intricacy of the chemokine system and explore its potential to guide the treatment of cancer and inflammation-related diseases.

2 | CHEMOKINE SYSTEMS

2.1 | The structure of chemokines

The chemokine network is composed of nearly 50 chemokine ligands, 20 GPCRs, and four ACKRs,¹⁷ which play significant roles in the body's immune homeostasis, inflammatory response, viral infection, and tumor progression (Figure 1). Most of the functional studies published in recent years have shown that the chemokine ligand axis conforms the classical GPCR activation paradigm.^{18–20} Once the ligand is stimulated, the G protein dissociates from the corresponding receptor and initiates different signaling events downstream of ligand binding that can eventually lead to various responses, such as cell proliferation, survival, invasion, migration, and gene transcription.^{28,17}

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FIGURE 1 The ligand-binding patterns of the seven-transmembrane domain G-protein-coupled chemokine receptors. The receptors CCR1–CCR5, CCR7, CCR8, CCR10, CXCR1–CXCR3, and CXCR7 all bind to multiple chemokines. In contrast, CCR6, CCR9, CXCR4–CXCR6, CX3CR1, and XCR1 each bind only one ligand. Four molecules are included in the atypical chemokine receptor (ACKR) family and boast high affinity to CC-/CXC- chemokines (the figure was created using biorender.com)

All chemokines are small, with approximately 20–50% identical sequences between individual chemokines, suggesting homology in their gene sequences and amino acid sequences.^{1,21} Typical chemokine proteins are synthesized as peptide precursors and during their secretion from cells, a signal peptide consisting of about 20 amino acids is split from the active part of the molecule. All chemokines possess conserved amino acid sequences, typically four cysteines that in most cases interact to form a Greek key shape, which is important for the formation of their three-dimensional or tertiary structure.²² The first two cysteines are close to the n-terminus of the maturing protein, the third cysteine is located in the middle of the molecule, and the fourth cysteine is near the Cterminus. After the first two cysteines, there is a ring of about 10 amino acids called the N ring. Chemokine receptors bind to G proteins and transmit cellular signals (Figure 2). When chemokines bind to the seven transmembrane GPCRs, they initiate the dissociation of G protein

subunits α and $\beta\gamma$, which subsequently leads to the activation of phospholipase C (PLC). PLC acts by splitting the phosphatidylinositol bisphosphate (PIP2) molecule into two second messenger elements, inositol triphosphate (IP3) and diacylglycerol (DAG). DAG then activates protein kinase C, whereas IP3 triggers the release of intracellular calcium ions, thereby driving cell polarization, adhesion, and migration. These events also trigger multiple intracellular signaling cascades (e.g., PI3K/AKT and JAK/STAT pathways) that impel activated signaling molecules into the nucleus to initiate transcriptional processes.^{8,17}

2.2 | The classification of chemokines and their receptors

According to the number and location of the highly conserved N-terminal cysteines, chemokines are grouped into four different subfamilies: CC, CXC, CX3C, XC, and



FIGURE 2 Chemokines/chemokine receptors signaling pathways. Chemokines transmit cellular signals by interacting with chemokine receptors, which are expressed on the cell surface as 7-transmembrane proteins. Almost all types of chemokines bind to the classical G protein-coupled receptor (GPCR), and activation of G proteins leads to subsequent activation of phospholipase C (PLC). PLC then cleaves a molecule called phosphatidylinositol-bisphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG); DAG activates protein kinase C, whereas IP3 triggers the intracellular release of stored calcium. Chemokines also activate the JAK/STAT, Ras/Raf/ERK, and PI3K/AKT signaling pathways through the GPCR signaling cascade. These events have an important role in cancer biology, involving tumor cell proliferation, invasion, metastasis, and angiogenesis. The atypical chemokine receptors (ACKRs) do not induce immune cell movement due to their structural inability to bind G proteins, rather their main function is to regulate the concentrations and bioavailability of chemokines on both sides of the cell membrane (the figure was created using biorender.com)

the nomenclature of the receptors is essentially similar to that of corresponding chemokines, that is, CC chemokine (CCL) binds to CC chemokine receptor (CCR) and CX3C ligand binds to CX3C receptor (CX3CR) (Table 1).²³⁻⁷⁰ Depending on their functions in the body, chemokines are also categorized into proinflammatory chemokines, homeostatic chemokines, or chemokines with both functions. Homeostatic chemokines, such as CCL17, CXCL14, and CXCL15, are produced constitutively in lymphocytes or other organs under normal biological conditions and are crucially important for immune surveillance because they primarily govern the homeostatic migration and homing of various immune cells.⁷¹ Inflammatory chemokines are induced by infection and other proinflammatory stimuli and their main function is to rapidly attract leukocytes to the site of infection or injury to act as inflammatory mediators.^{71–73} Chemokines can also be subdivided into the following categories according to the different cells on which they act. (1) monocyte/macrophage chemokines function as key chemokines to attract monocytes/macrophages to sites of inflammation, including CCL2-3, CCL5, CCL7-8, CCL13, CCL17, and CCL22.74-77 (2) T lymphocyte chemokines include four chemokines implicated in the recruiting of T lymphocytes to sites of inflammation: CCL1, CCL2, CCL17, and CCL22. In addition, activated T cells induce the expression of CXCR3 and secretion of interferon (IFN)-y-induced

chemokines CXCL9–11 at sites of inflammation.⁷⁸ (3) Mast cell chemokines express multiple chemokine receptors on their surface including CCR1-5, CXCR2, and CXCR4.79,80 CCL2 and CCL5, as ligands for these receptors, play a pivotal role in the recruitment and activation of lung mast cells. (4) Eosinophil chemokines direct the migration of eosinophils to different tissues chiefly involved in several chemokines of the CC subfamily: CCL3, CCL5, CCL7, CCL11, CCL13, CCL24, and CCL26.81,82 Eosinophils are among the first immune cells to be recruited to the lesion, where the chemokines CCL5 and CCL11 act by binding to CCR3 that is expressed on the surface of eosinophils.83 (5) Neutrophil chemokines are primarily CXC types of chemokines. For example, CXCL8 (interleukin [IL]-8) in the TME is a chemotactic agent for neutrophils, inducing neutrophils into TME and activating their metabolism and degranulation.^{84–86}

3 | DIFFERENT CHEMOKINE AXES

Although a chemokine may bind to multiple receptors, when it binds to a specific receptor and exhibits excitatory effects on the binding site and antagonistic effects on other bindings, the chemokine and its receptor form a functional chemokine axis.⁸⁷ Below, we will summarize the characteristics of eight most reported chemokine axes, as well

TABLE 1 The chemokine s:	ubfamilies and their rece	ptors		
Class	Systemic name	Synonym	Receptor	Function
CXC (α subfamily)	CXCL1 ²³	Growth-regulated protein-α (GROα), Gro-oncogene 1 (GRO1), neutrophil-activating protein-3, and keratinocyte-derived chemokine	CXCR2	Inflammatory
	CXCL2 ²⁴	Macrophage inflammatory protein-2a (MIP-2α), GROβ, Gro2	CXCR2	Inflammatory
	CXCL3 ²⁵	MIP-2 β , GRO γ , Gro 3	CXCR2	Inflammatory
	CXCL4 ²⁶	Platelet factor 4 (PF4)	Unknown	Unknown
	CXCL5 ²⁷	Epithelial-derived neutrophil-activating peptide 78 (ENA-78)	CXCR2 and DARC	Inflammatory
	CXCL6 ²⁸	Granulocyte chemotactic protein-2 (GCP-2)	CXCR1, CXCR2	Inflammatory
	CXCL7 ²⁹	Platelet basic protein (PBP), leukocyte-derived growth factor (LDGF), macrophage-derived growth factor (MDGF), Small-inducible cytokine B7	CXCR2	Inflammatory
	CXCL8 ³⁰	Interleukin-8 (IL-8), T-cell chemotactic factor, lymphocyte derived neutrophil activating peptide (LYNAP), neutrophil activating peptide-1 (NAP-1)	CXCR1, CXCR2	Inflammatory
	CXCL9 ³¹	Monokine induced by gamma interferon (MIG)	CXCR3 and CXCR3B	Inflammatory
	CXCL10 ³²	Interferon (IFN)- <i>y</i> -induced protein 10 (IP-10), small inducible cytokine B10	CXCR3 and CXCR3B	Dual: adaptive immunity (Th1 responses)
	CXCL11 ³³	IP-9, interferon-inducible T-cell α-chemoattractant (I-TAC)	CXCR3, CXCR3B, and CXCR7	Inflammatory
	CXCL12 ³⁴	Stromal cell-derived factor-1 (SDF-1), SDF-1 α	CXCR4 and CXCR7	Homeostatic
	CXCL13 ³⁵	B-lymphocyte chemoattractant (BLC)	CXCR5 and CCXCKR	Homeostatic
	CXCL14 ³⁶	Breast- and kidney-expressed chemokine	Unknown	Inflammatory: development of antigen-presenting cells
	CXCL15 ³⁷	Lungkine	CXCR2	Unknown
	CXCL16 ³⁸		CXCR6	Inflammatory: T lymphopoiesis, extravasation
	CXCL17 ³⁹	Dendritic and monocyte chemokine-like protein, vascular endothelial growth factor (VEGF)-coregulated chemokine-1	Unknown	Unknown
				(Continues)

	Systemic			
Class	name	Synonym	Receptor	Function
CC (β subfamily)	CCL1 ⁴⁰	Inflammatory cytokine I-309	CCR8	Inflammatory
	CCL2 ⁴¹	Monocyte chemotactic protein-1 (MCP-1) and small inducible cytokine A2	CCR2	Inflammatory: innate and adaptive immunity
	CCL3 ⁴²	MIP-1α	CCR1 and CCR5	Inflammatory
	CCL4 ⁴³	MIP-1ß	CCR5	Inflammatory
	CCL5 ⁴⁴	Regulated on activation, normal T-cell expressed and secreted (RANTES)	CCR1, CCR3, and CCR5	Inflammatory
	CCL6 ⁴⁵	Macrophage inflammatory protein-related protein-1 (MRP-1)	CCRI	Unknown
	CCL7 ⁴⁶	MCP-3	CCR1, CCR2, and CCR3	Inflammatory
	CCL8 ^{47,52}	MCP-2	CCR1, CCR2, CCR3, and CCR5	Inflammatory
	CCL9 ⁴⁸	MIP-17, MRP-2	CCR1	Inflammatory
	CCL10 ⁴⁹	Unknown	Unknown	Unknown
	CCL11 ⁵⁰	Eotaxin	CCR3	Inflammatory
	CCL12 ⁵¹	MCP-5	CCR2	Inflammatory
	CCL13 ⁵²	MCP-4	CCR1, CCR2, CCR3, and CCR5	Inflammatory
	CCL14 ⁵³	Hemofiltrate CC chemokine-1 (HCC-1)	CCR1 and CCR5	Homeostatic
	CCL15 ⁵⁴	Leukotactin-1, MIP-5, and HCC-2	CCR1 and CCR3	Homeostatic
	CCL16 ⁵⁵	Monotactin-1, liver-expressed chemokine, and HCC-4	CCR1, CCR2, CCR5, and CCR8	Homeostatic
	CCL17 ⁵⁶	Thymus- and activation-regulated chemokine (TARC)	CCR4	Dual
				(Continues)

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	Systemic			
Class	name	Synonym	Receptor	Function
	CCL18 ²⁷	MIP-4, pulmonary- and activation-regulated chemokine (PARC), alternative macrophage activation-associated CC chemokine 1 (AMAC-1)	Unknown	Homeostatic: T cell-dendritic cell interaction (spleen, lymph node)
	CCL19 ⁵⁸	MIP-3 β , EBl1 ligand chemokine (ELC) exodus-3	CCR7 and CCXCKR	Homeostatic: T lymphopoiesis
	CCL20 ^{52,59}	MIP-3α, liver activation-regulated chemokine (LARC), exodus-1	CCR6	Dual: development of dendritic cells, adaptive immunity
	CCL21 ⁶⁰	Secondary lymphoid tissue chemokine (SLTC), exodus-2, TCA4	CCR7 and CCXCKR	Dual: spleen and lymph node T cell homing
	CCL22 ⁶¹	Macrophage-derived chemokine (MDC)	CCR4	Dual: adaptive immunity (cutaneous T cells)
	CCL23 ⁶²	MIP-3, myeloid progenitor inhibitory factor-1 (MPIF-1)	CCR1	Inflammatory
	CCL24 ⁶³	Eotaxin-2, MPIF-2	CCR3	Inflammatory
	CCL25 ⁶⁴	Thymus-expressed chemokine (TECK)	CCR9 and CCXCKR	Dual: T lymphopoiesis, adaptive immunity, T cell and B cell trafficking in small intestine
	CCL26 ⁶⁵	MIP-4 α , eotaxin-3, thymic stroma chemokine-1	CCR3	Inflammatory
	CCL2766	Cutaneous T-cell-attracting chemokine (CTACK), IL-11 receptor a-locus chemokine (ILC), embryonic stem cell chemokine	CCR10	Homeostatic
	CCL28 ⁶⁷	Mucosae-associated epithelial chemokine (MEC)	CCR3 and CCR10	Homeostatic
XC (γ subfamily)	XCL1 ⁶⁸	Lymphotactin $lpha$	XCR1	Dual
	XCL2 ⁶⁹	Lymphotactin eta	XCR2	Dual
CX3C (δ subfamily)	CX3CL1 ⁷⁰	Fractalkine, neurotactin	CX3CR1	Inflammatory: extravasation

as recent advances in these chemokine axes in cancer and inflammatory diseases.

3.1 | The CCL2/CCR2 axis

3.1.1 | Brief introduction to the CCL2/CCR2 signaling axis

CCL2 belongs to the CC chemokine subfamily, also known as small inducible cytokine A2 and monocyte chemotactic protein-1 (MCP-1). As the most well-studied chemokine, CCL2 was originally identified in 1989 from the culture supernatant of peripheral blood monocytes and tumor cell lines.^{88,89} CCL2 was at first characterized as a "tumorderived chemokine" and has been documented to be a potent chemotactic agent for a couple of immune cells (e.g., monocytes, immature dendritic cells (DCs), memory T cells, and natural killer (NK) cells), thereby promoting inflammatory effects and neoangiogenesis. In addition, various stromal cells in the TME, including endothelial cells, DCs, fibroblasts, and adipocytes, are capable of producing CCL2 to promote tumor growth and progression.^{90–92} CCL2 was the first CC chemokine to be identified and fully studied and has a high affinity for its receptor, CCR2. It has been revealed that CCR2 is widely expressed in a broad range of cell types, including monocytes,93 endothelial cells,94 DCs,95 and various cancer cells and the upregulation of CCR2 is related to advanced cancer, metastasis, and relapse.⁹⁶ Once bound to its ligand CCL2, the activated signaling axis triggers various intracellular G protein-mediated signaling cascades, such as mitogen-activated protein kinase (MAPK)/p38, PI3K/AKT, and JAK/STAT3 pathways.^{97–99} The CCL2/CCR2 axis is implied in the proliferation, invasion, and angiogenesis of tumor cells and recruitment of immunosuppressive cells.^{100,101} Previous data also identified a regulatory role of the CCL2/CCR2 signaling axis on the nervous system.¹⁰² Microglia are the resident immune cells of the central nervous system (CNS), which is phylogenetically related to monocytes and therefore also expresses CCR2. CCL2 can also be produced by microglia/macrophages or endothelial cells under basal and neuroinflammatory conditions.^{103,104} Typically, CCL2 secreted by activated astrocytes (the major glial cells of the CNS) is thought to attract microglia to sites of neuronal infection or injury, where they engulf microbes or cellular debris.¹⁰⁵ The relationship between the CCL2/CCR2 signaling axis and the pathogenesis of autoimmune diseases has also been widely investigated, and a common pathological feature of these autoimmune diseases is the upregulation of CCL2 and/or CCR2 expression in the lesions.^{106,107}

3.1.2 | Roles of the CCL2/CCR2 signaling axis in tumor progression

It has been demonstrated that CCL2 and its receptor CCR2 are implicated in the development and progression of various malignancies, such as prostate cancer,¹⁰⁸ breast cancer,¹⁰⁹ hepatocellular cancer,¹¹⁰ lung cancer,¹¹¹ renal cancer,¹¹² pancreatic cancer,¹¹³ and nasopharyngeal carcinoma.¹¹⁴ The CCL2/CCR2 signaling axis is involved in different stages of tumorigenic progression, for example, maintaining the proliferation and stemness of tumor cells at the site of the primary tumor; and when malignant cells metastasize, promoting the invasion of cancer cells into surrounding tissues and circulatory system, and traveling down a specific chemotactic ladder to the site of metastasis (Figure 3).96 After reaching a new organ and/or tissue, residual circulating tumor cells are able to successfully colonize and continue to grow through interactions with various components within the TME.⁹¹ It has been suggested that CCL2 might act as an autocrine or paracrine chemokine to promote the growth of tumor cells, which can be partially abolished by CCR2 antagonists or PI3K inhibitors.¹¹⁵ CCL2 can promote drug resistance in gastric cancer cells by inhibiting autophagy, and either knockdown of CCL2 or induction of autophagy successfully reversed drug resistance in tumor cells.¹¹⁶ Similarly, in vitro experiments showed that downregulation of CCL2 decreased the viability of A549 cells and enhanced docetaxel (DTX)-induced cytotoxicity, whereas upregulation of CCL2 protected A549 cells from DTX-induced cytotoxicity.¹¹⁷ The chemoresistance that occurs within lung cancer cells may be mediated by the stress response of CCL2-expressing cells, implicating CCL2 as a possible target for augmenting the therapeutic efficacy of DTX on lung cancer.¹¹⁷ CCL2 also attracts different immune cells to form an immunosuppressive microenvironment, which promotes the formation of tumor-associated microvasculature and supports the growth and metastasis of tumor cells. In mouse melanoma and pancreatic cancer models, knockdown of CCL2 with siRNA or antibody neutralization effectively inhibited DC recruitment, reduced CD68+ macrophage infiltration, and decreased tumor growth and metastasis.^{118–120} Furthermore, radiotherapy induces a significant increase in the recruitment of CCL2 and Ly6C⁺CCR2⁺ monocytes in pancreatic ductal adenocarcinoma (PDAC), thereby accelerating tumor proliferation and angiogenesis. Anti-CCL2 antibodies selectively inhibit radiotherapy-dependent monocyte/macrophage recruitment and retard tumor growth when used in combination with radiotherapy.¹²¹ However, several studies have shown inconsistent results and thereby different conclusions. Fader et al.¹²² included 37 patients with primary

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FIGURE 3 Chemokines/chemokine receptors in tumor immune microenvironment and their relevance in cancer immunotherapy. Immune cell populations, such as monocytic and granulocytic myeloid-derived suppressor cells (MDSCs), plasmacytoid dendritic cells (DCs), regulatory T (Treg) cells, and IL-22⁺CD4⁺ T helper 22 cells can promote tumor growth. Immune cells, such as T helper 17 cells, T helper 1 cells, CD8+ T cells, and natural killer cells (NK cells), have antitumor effects. These cells are recruited to the tumor, particularly the tumor immune microenvironment through chemokine/chemokine receptor signaling axes and are involved in almost all aspects of the tumor progression (e.g., tumor proliferation, angiogenesis, and metastasis) (the figure was created using biorender.com)

ovarian cancer to investigate the relationship between CCL2 expression in tumor specimens and patient response to chemotherapy and survival outcomes. The results suggested that increased expression of CCL2 in ovarian tumors was associated with better chemotherapy response and improved survival outcomes. Also, in vitro experiments illustrated that ovarian cancer cells with higher CCL2 expression were more sensitive to the traditional chemotherapeutic drugs paclitaxel and cisplatin.¹²² Interestingly, recent evidence indicates that higher levels of CCL2 in patients with squamous lung cancer is related to favorable progression-free survival (PFS) and overall survival (OS); however, lung adenocarcinoma patients with a high expression of CCL2 exhibited a shorter OS and PFS than those with a low expression.¹²³ Moreover, in vitro data from one study indicated that CCL2 could activate neutrophils and mediate the killing of breast cancer cells, whereas in mice breast cancer models, intranasal administration of CCL2 protein was able to increase the recruitment of CD4+ T cells in the lung, favoring tumor dissemination, and metastasis to the lung.¹²⁴

Taken together, the CCL2/CCR2 signaling axis is involved in a wide range of tumor cell activities, and regulation of CCL2 and/or CCR2 expression influences tumor progression. Deeper insight into the potential mechanisms of the CCL2/CCR2 axis in tumor progression and treatment will provide new directions for a better understanding of malignancies.

3.1.3 | The CCL2/CCR2 axis in autoimmune diseases and neurological disorders

The pathology of autoimmune diseases is characterized by the infiltration of multiple lymphocytes in the tissues, which leads to inflammation and tissue damage. This process involves a complex network of immune cells in which chemokines act as signaling bridges. Many studies have elucidated monocytes as the molecular basis of immune cells recruitment in autoimmune disease, suggesting a major role for CCL2 and its cell surface receptor CCR2.^{107,125-127} Psoriasis is a chronic skin disease caused by an imbalance between skin keratinocytes and infiltrating immune cells. In patients with psoriasis, keratinocytes secrete large amounts of CCL2, which, when combined with CCR2 on the surface of monocytes, can induce monocytes to differentiate into macrophages and migrate from the bloodstream to the site of inflammation.¹²⁸ CCL2 is an emerging novel target in systemic lupus erythematosus (SLE) and lupus nephritis, in which the CCL2/CCR2 axis mediates the infiltration of macrophages and T cells into the nephron in nephritis.¹²⁹ Moreover, a meta-analysis covering 399 patients with lupus nephritis and 130 normal controls revealed that urinary CCL2 was markedly higher in patients with active lupus nephritis than those with inactive lupus nephritis and controls, suggesting that urinary CCL2 might serve as a biomarker for lupus nephritis.¹³⁰ Meanwhile, in vivo experimental studies have illustrated that blocking CCL2 was effective in inhibiting the progression of proliferative lupus nephritis.¹³¹

Given the possibility that the CCL2/CCR2 axis may exert a range of immune regulation on the nervous system, its proinflammatory properties were subsequently thought to be a leading factor in the evolution of depression. Studies carried out by Stuart et al.¹³² have shown that the CCL2/CCR2 axis might be involved in regulating the proliferation and differentiation of neural progenitor cells, modulating the infiltration and activation of central immune cells, and influencing the secretion of proinflammatory factors (e.g., IL-1 β and IL-8). Many scientists and histologists have argued that elevated CCL2 levels lead to increased blood–brain barrier permeability by inducing macrophage recruitment, cytokine production, and directly altering endothelial cell tight junction protein expression, which are observed in a variety of pathological processes, such as neuroinflammation,¹³³ stroke,¹³⁴ MS,¹³⁵ and Alzheimer's disease (AD).¹³⁶

The infection of HIV causes chronic inflammation in the body, along with a dysregulated immune system, which further exacerbates the inflammatory response.^{137,138} The interaction of chemokine receptors (for example, CCR2, CCR3, CCR5, and CXCR4) on the cell surface with external components of HIV and accessory proteins is an essential step in HIV infection of target cells.^{139,140} Among them, CCR5 and CXCR4 are the primary coreceptors for HIV-1 invasion into target cells, with CCR2 and CCR3 playing secondary synergistic roles.¹⁴¹ In HIV infection, accentuated expression of CCL2 and/or CCR2 may contribute to HIV-associated complications in multiple ways, depending on their role in leukocytes recruitment and maintenance of an inflammatory state.¹⁴² Apart from its role in inflammation and cell-directed migration, however, CCL2 has been proven to influence directly viral replication, as evidenced by studies performed in peripheral blood mononuclear cells, T lymphocytes, and macrophages.^{143–145} Recently, several attempts have been made to investigate the relationship between high expression of CCL2 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.146,147 Conclusively, targeting the CCL2/CCR2 axis is considered to be an attractive target for the treatment of autoimmune diseases and viral infections. Therefore, more attention should be paid in the future to comprehensively investigate the potential mechanisms of action of the CCL2/CCR2 axis in these diseases mentioned above.

3.1.4 | Clinical trials of drugs targeting the CCL2/CCR2 axis

Due to the pivotal role played by the CCL2/CCR2 signaling axis in the progression of multiple diseases, a host of clinical trials of drugs that modulate this axis have been continually launched (Table 2). Currently, clinical trials of human neutralizing antibodies against CCL2 are focused on carlumab and MLN1202 that can effectively block the differentiation of monocytes to macrophages and reduce immune cell recruitment after binding to CCL2, exhibiting broad anti-tumor effects. In a phase I study evaluating the safety and antitumor activity

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Target	Drug name	Conditions	Phase	Status	Trial number
CCL2	Carlumab	Metastatic castrate-resistant prostate cancer	Π	Completed	NCT00992186
	Carlumab	Solid tumors	Ι	Completed	NCT00537368
	Carlumab	Combination with chemotherapy in patients with solid tumors	Ι	Completed	NCT01204996
CCR2	MLN1202	Cancer with bone metastases	II	Completed	NCT01015560
	MK-0812	Multiple sclerosis	Π	Terminated	NCT00239655
	MK-0812	Rheumatoid arthritis	Π	Completed	NCT00542022
	CCX872-B	Pancreatic adenocarcinoma	Ι	Not recruiting	NCT02345408
	JNJ-41443532	Type 2 diabetes mellitus	Π	Completed	NCT01230749
	JNJ-17166864	Allergic rhinitis	II	Completed	NCT00604123
	AZD2423	Chronic obstructive pulmonary disease	П	Completed	NCT01215279
	AZD2423	Chronic obstructive pulmonary disease	Π	Completed	NCT01153321
	AZD2423	Painful diabetic polyneuropathy	Π	Completed	NCT01201317
	AZD2423	Posttraumatic neuralgia	Π	Completed	NCT01200524
	CCX872-B	Combination with preoperative radiation therapy in pancreatic adenocarcinoma	П/П	Withdrawn	NCT03778879
	PF-04136309	Advanced pancreatic adenocarcinoma	Ι	Completed	NCT01413022
	PF-04136309	Combination with gemcitabine and nab-paclitaxel in metastatic pancreatic adenocarcinoma	н	Terminated	NCT02732938
CCR5	Maraviroc	Kaposi's sarcoma	Π	Completed	NCT01276236
	Maraviroc	Hematologic malignancy	Π	Completed	NCT01785810
	Maraviroc	Colorectal cancer	Ι	Completed	NCT01736813
	Maraviroc	Combination with pembrolizumab in metastatic colorectal cancer	ц	Completed	NCT03274804
	Maraviroc	Graft-versus-host disease	I/II	Completed	NCT00948753
	Maraviroc	Hypertriglyceridemia	Ι	Completed	NCT01133210
					(Continues)

TABLE 2 Overview of clinical trials targeting chemokines and their receptors

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Target	Drug name	Conditions	Phase	Status	Trial number
	Maraviroc	Combination with rehabilitation therapy in stroke	111/11	Recruiting	NCT03172026
	Maraviroc	COVID-19	Ι	Completed	NCT04435522
	Vicriviroc	Combination with pembrolizumab in colorectal neoplasms	П	Active, not recruiting	NCT03631407
	Vicriviroc	HIV infections, acquired immunodeficiency syndrome	III	Withdrawn	NCT00243568
	Leronlimab	Solid tumors	III	Completed	NCT04504942
	Leronlimab	Nonalcoholic steatohepatitis	Π	Recruiting	NCT04521114
	Leronlimab	COVID-19	II	Recruiting	NCT04347239
	Leronlimab	Combination with carboplatin in CCR5+ triple negative breast neoplasm	П/П	Recruiting	NCT03838367
	AZD5672	Rheumatoid arthritis	II	Completed	NCT00713544
	Lentivirus vector rHIV7-shI-TAR- CCR5RZ-transduced hematopoietic progenitor cells	Intermediate-grade or high-grade AIDS-related lymphoma	ц	Completed	NCT00569985
CCR2/ CCR5	BMS-813160	Combination with GVAX for locally advanced pancreatic ductal adenocarcinoma (PDAC)	1/1	Recruiting	NCT03767582
	BMS-813160	Combination with nivolumab, gemcitabine, and nab-paclitaxel in borderline resectable and locally advanced PDAC	1/1	Recruiting	NCT03496662
	BMS-813160	Combination with chemotherapy or nivolumab in patients with pancreatic cancer	П/П	Not recruiting	NCT03184870

TABLE 2 (Continued)

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(Continues)

TABLE 2 (Continued)					
Target	Drug name	Conditions	Phase	Status	Trial number
	BMS-813160	Advanced renal cell carcinoma	Π	Recruiting	NCT02996110
	BMS-813160	Hepatocellular carcinoma	Π	Recruiting	NCT04123379
	Cenicriviroc	COVID-19	II	Recruiting	NCT04500418
	Cenicriviroc	Nonalcoholic steatohepatitis	Π	Completed	NCT03517540
	Cenicriviroc	Nonalcoholic steatohepatitis	II	Completed	NCT02217475
	Cenicriviroc	Liver insufficiency	Ι	Completed	NCT02120547
	Cenicriviroc	Prediabetic state, nonalcoholic fatty liver disease, type 2 diabetes mellitus	П	Completed	NCT02330549
	Cenicriviroc	Primary sclerosing cholangitis	Π	Completed	NCT02653625
	Cenicriviroc	Hepatic impairment	Ι	Completed	NCT03376841
CCL21	CCL21 protein	Combination with GM.CD40L vaccine in stage IV lung adenocarcinoma	1/1	Completed	NCT01433172
	CCL21-Gene-modified dendritic cell vaccine	Combination with pembrolizumab stage IV nonsmall cell lung cancer	ц	Recruiting	NCT03546361
	Autologous dendritic cell-adenovirus CCL21 vaccine	Melanoma (Skin)	Ι	Completed	NCT00798629
	Autologous dendritic cell-adenovirus CCL21 vaccine	Advanced or recurrent nonsmall cell lung cancer	Ι	Completed	NCT00601094
CCR7	CD4 + CCR7 +T lymphocytes	Acute myeloblastic leukemia	Not Applicable	Completed	NCT03280290
	JBH492	Relapsed/refractory chronic lymphocytic leukemia and non-Hodgkin's lymphoma	I/Ib	Recruiting	NCT04240704
CCL20	GSK3050002	Ulcerative colitis	Ι	Completed	NCT01984047
	AZD0284	Plaque psoriasis vulgaris	Ι	Terminated	NCT03310320
					(Continues)

TABLE 2 (Continued)					
Target	Drug name	Conditions	Phase	Status	Trial number
CXCL5	Immunohistochemical expression of CXCL5	Urinary bladder urothelial carcinoma	Not Applicable	Recruiting	NCT05139134
	Sunitinib malate	Kidney cancer	Not Applicable	Completed	NCT00943839
CXCR2	AZD5069	Neutrophil number and function study	Ι	Completed	NCT01480739
	AZD5069	Combination with enzalutamide in metastatic castration resistant prostate cancer	Π/Ι	Recruiting	NCT03177187
	Navarixin	Combination with pembrolizumab advanced/metastatic solid tumors	п	Completed	NCT03473925
	Navarixin	Psoriasis	II	Completed	NCT00684593
	Navarixin	Allergen-induced asthma	II	Completed	NCT00688467
	Navarixin	Chronic obstructive pulmonary disease	П	Terminated	NCT01006616
	CXCR2 ligands/CXCR2	Biological axis in pancreatic cancer	Not Applicable	Completed	NCT00851955
	RIST4721	Inflammatory response	Ι	Completed	NCT04105959
	CXCR2-transduced autologous tumor infiltrating lymphocytes	Metastatic melanoma	II/I	Active, not recruiting	NCT01740557
	GSK1325756	Chronic obstructive pulmonary disease	Ι	Completed	NCT01209052
	GSK1325756	Nutritional status	Ι	Completed	NCT01209104
	Danirixin	Chronic obstructive pulmonary disease	Ι	Completed	NCT03136380
	Danirixin	Chronic obstructive pulmonary disease	Π	Terminated	NCT03250689
	Danirixin	Chronic obstructive pulmonary disease	Π	Completed	NCT03034967
	Danirixin	Infections, respiratory syncytial virus	Ι	Completed	NCT02201303

(Continues)

TABLE 2 (Continued)					
Target	Drug name	Conditions	Phase	Status	Trial number
	Danirixin	Chronic obstructive pulmonary disease	Π	Completed	NCT02130193
	SB-656933-AAA	Chronic obstructive pulmonary disease	Ι	Completed	NCT00504439
CXCL9	Emapalumab	Hemophagocytic lymphohistiocytoses	11/11	Active, not recruiting	NCT03985423
	Emapalumab	Graft failure	Π	Recruiting	NCT04731298
CXCL10	NI-0801	Primary biliary cirrhosis	Π	Terminated	NCT01430429
	MDX-1100	Combination with methotrexate in rheumatoid arthritis	П	Completed	NCT01017367
	MDX-1100	Ulcerative colitis	Ι	Completed	NCT00295282
	MDX-1100	Ulcerative colitis	Π	Completed	NCT00656890
	CXCL10 protein	COVID-19	Not Applicable	Completed	NCT04389645
CXCL10/CXCR3	Ozone	Environmental and genetic factors on lung function	Early Phase I	Recruiting	NCT03599206
CXCL12	JVS-100	Peripheral arterial disease	Π	Unknown	NCT02544204
	JVS-100	Critical limb ischemia	Π	Completed	NCT01410331
	ACRX-100	Heart failure	Ι	Completed	NCT01082094
	NOX-A12	Combination with irradiation in glioblastoma	11/1	Recruiting	NCT04121455
	NOX-A12	Combination with pembrolizumab in colorectal and pancreatic cancer	11/1	Completed	NCT03168139
	NOX-A12	Combination with bortezomib and dexamethasone in relapsed multiple myeloma	Π	Completed	NCT01521533
	NOX-A12	Combination with bendamustine and rituximab in relapsed chronic lymphocytic leukemia	П	Completed	NCT01486797
	NOX-A12	Hematopoietic stem cell transplantation	Ι	Completed	NCT01194934
CXCR4	AMD3100	Healthy volunteers	Ι	Completed	NCT00322127
	AMD3100	Neutropenia	I	Completed	NCT01058993
					(Continues)

TABLE 2 (Continued)					
Target	Drug name	Conditions	Phase	Status	Trial number
	AMD3100	Acute myeloid leukemia	I/I	Completed	NCT00512252
	AMD3100	Lymphoma	I/I	Completed	NCT00733824
	AMD070	HIV Infections	Ι	Completed	NCT00063804
	POL6326	Healthy volunteers	Ι	Completed	NCT01841476
	CXCR4 modified anti-BCMA (B-cell maturation antigen) CAR T cells	Multiple myeloma	Early Phase I	Not yet recruiting	NCT04727008
	POL6326	Large reperfused ST-elevation myocardial infarction	Π	Completed	NCT01905475
	BL-8040	Chronic myeloid leukemia	II/I	Withdrawn	NCT02115672
	BKT140	Multiple myeloma	I/I	Completed	NCT01010880
	Autologous CD4 T-cells	HIV infections	Early Phase I	Completed	NCT03020524
	AMD11070	HIV infections	II/I	Completed	NCT00089466
	AC220	Acute myeloid leukaemia, high risk myelodysplastic syndrome	11/1	Completed	NCT01236144
	BL-8040	Combination with pembrolizumab in metastatic pancreatic adenocarcinoma	П	Active, not recruiting	NCT02907099
	ALX-0651	Healthy volunteers	Ι	Terminated	NCT01374503
	BMS-936564	Multiple myeloma	Ι	Completed	NCT01359657
	BMS-936564	Acute myelogenous leukemia and selected B-cell cancers	Ι	Completed	NCT01120457
	LY2510924	Solid tumor	Ι	Terminated	NCT02737072
	USL311	Solid tumors, relapsed/recurrent glioblastoma multiforme	11/1	Terminated	NCT02765165
CXCL12/CXCR4	Tipifarnib	Relapsed or refractory peripheral T-cell lymphoma	Π	Completed	NCT02464228
CXCR5	CXCR5 modified EGFR CAR-T cells	Nonsmall cell lung cancer	Early phase I	Recruiting	NCT05060796
	SP01A	HIV infections	I/II	Completed	NCT00299338

Data from https://clinicaltrials.gov/.

of carlumab in advanced solid tumors (NCT00537368), 44 subjects were enrolled. Carlumab was shown to be well tolerated by all patients, as no carlumab-related adverse events were observed. However, durable stable disease (SD) was observed in only four of 33 evaluable patients, and none achieved an objective response (OR).¹⁴⁸ In another completed phase II study of carlumab monotherapy for metastatic castration-resistant prostate cancer (NCT00992186), none had an OR to carlumab treatment and only 34% of patients maintained SD for over 3 months. Notably, no patient generated antibodies to carlumab, although inhibition of free CCL2 serum concentrations was observed transiently after each dose, which seems unsustainable.¹⁴⁹ Similarly, in an open-label, multicenter phase 1b study of carlumab in combination with chemotherapy for advanced solid tumors (NCT01204996), researchers found that carlumab could be safely used in combination with standard chemotherapy doses at 10 or 15 mg/kg and was well tolerated, but did not suppress serum CCL2 levels or produce a significant antitumor response over time,¹⁵⁰ suggesting that effects are not apparent and further clarification is a necessity. Meanwhile, the efficacy of MLN1202 in 44 patients with bone metastases was studied in a phase II clinical trial (NCT01015560). Of the 41 patients who completed treatment, 7.14% experienced serious adverse effects and fourteen patients experienced a decrease in urinary N-terminal peptide values (an indicator of efficacy assessment), indicating a positive antitumor metastatic effect of MLN1202. MLN1202 was also used in randomized, double-blind, placebo-controlled studies of atherosclerotic cardiovascular disease and RA. The results showed that MLN1202 treatment was well tolerated and resulted in a significant reduction of highsensitivity C-reactive protein levels in serum,¹⁵¹ but did not lead to amelioration of synovial inflammation in active RA.¹⁵²

Inhibitors against CCR2 are designed to disrupt the binding of CCR2 to its ligand CCL2, acting by blocking the activation of a series of signaling cascades downstream of the CCL2/CCR2 axis. A phase I study evaluated the CCR2 inhibitor PF-04136309 in combination with FOLFIRINOX for the treatment of patients with advanced pancreatic cancer (NCT01413022). Among patients who completed a course of combination therapy, 97% achieved local tumor control and 49% achieved an objective tumor response. More importantly, the mean percentage of CCR2⁺ monocytes in the blood of the combination-treated patients was significantly lower compared with the chemotherapy group, suggesting that chemotherapy plus PF04136309 prevents the drainage of CCR2⁺ monocytes into the peripheral circulation from the bone marrow and affects antitumor immunity.¹⁵³ Both CCX140-B and CCX872-B can selectively inhibit CCR2 and are mainly used to evaluate the effect on type 2 diabetes.^{154,155} Several

other CCR2 inhibitors (e.g., MK-0812, JNJ-41443532, JNJ-17166864, AZD2423, etc.) have also been studied in clinical trials for CCL2/CCR2 axis-related diseases, showing a favorable safety profile.^{113,154,156-159}

3.2 | The CCL5/CCR5 axis

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3.2.1 | Characteristics of the CCL5/CCR5 signaling axis

When CCL5 (also known as RANTES: regulated upon activation normal T cell expressed and secreted) was first identified, it appeared to be a classic chemokine because of its ability to direct leukocytes to sites of inflammation. It has been well accepted that CCL5 can be secreted by most inflammatory cells, with monocytes and T cells being the most common sources of CCL5.¹⁶⁰ Although CCL5 can bind to several receptors, such as CCR1, CCR3-5, CD44, and GPR75, it has the highest affinity to CCR5.¹⁶¹ The transcription of CCR5 (also known as CD195) is regulated by CREB-1 and mRNA and protein expression are commonly observed in T-lymphocytes, monocytes, macrophages, immature DCs, eosinophils, and microglia.^{162,163} CCL5 is not the only ligand for CCR5 since CCR5 also binds to proteins with an N-terminal extracellular tail, such as CCL3 (macrophage inflammatory protein [MIP]-1 α) and CCL4 (MIP-1 β).¹⁶³ Furthermore, CCR5 on the surface of CD4⁺ T cells is the most prominent coreceptor that assists HIV-1 to infect cells through binding to GP120, therefore it is considered a prospective candidate for anti-HIV therapies.¹⁶⁴ The CCL5/CCR5 axis has also been reported to be engaged in the activation of several signaling pathways, including JAK/STAT, PI3K/AKT/mTOR, HIF- α , TGF- β -smad, and NF- κ B axes that are implicated in inflammation, angiogenesis, tumor cell proliferation, apoptosis, and metastasis.¹⁶⁵⁻¹⁶⁷ In the TME, increased CCR5 levels may be the result of high CCR5 expression on the tumor cell surface or the aggregation of CCR5⁺ cells, such as monocytes, lymphocytes, adipocytes, and mesenchymal stem cells (MSCs).¹⁶¹

3.2.2 | The role of CCL5/CCR5 axis in cancer progression

The overexpression of CCL5 and/or its receptor CCR5 in various tumor cells (e.g. breast cancer,¹⁶⁸ acute lymphocytic leukemia,¹⁶⁹ multiple myeloma (MM),¹⁷⁰ Hodgkin lymphoma,¹⁷¹ colorectal carcinoma¹⁷²) has long been elucidated. The expression of CCL5 is rare in normal ductal epithelium or benign breast tumor masses, but can be obtained during malignant transformation of cells.¹⁷³ Additionally, CCL5 is highly expressed in advanced triple-negative breast cancer,¹⁷⁴ whereas CCL5 is not overexpressed in breast tissue from women with benign breast disease or those who have undergone breast reduction.¹⁶⁸ In vivo studies demonstrate that breast cancer cells stimulate MSCs to resecrete CCL5, which then acts in a paracrine manner on tumor cells. These researchers also found that lung metastasis and colonization of tumor cells increased after mice were given both breast cancer cells and MSCs, suggesting that CCL5 facilitates the metastatic ability of tumor cells.¹⁷⁵ The CCL5/CCR5 axis also has far-reaching impact on the progression of hematologic malignancies. For example, higher levels of CCL5 are detected in the serum of patients with acute myeloid leukemia, who have a monocytic phenotype¹⁷⁶ or Fms-like tyrosine kinase 3-internal tandem duplication mutations.¹⁷⁷ Also, CCL5 secretion is increased when CD40 is cocultured with classical Hodgkin lymphoma cells or with MSCs derived from lymph nodes of Hodgkin lymphoma patients.¹⁷⁸ High levels of CCL5 in Hodgkin's lymphoma tissue are correlated with monocyte infiltration and poor prognosis.¹⁷¹ In addition, in vivo studies have shown that inhibition of CCR5 by neutralizing antibodies or antagonists was able to retard the progression of MM, reduce osteolytic lesions, and inhibit osteoclastogenesis.^{179,180} CCL5 and CCR5 are overexpressed in colorectal cancer (CRC) primary tumor cells as well as in metastasis cells of the liver and lung and are positively correlated with prognosis in CRC.¹⁸¹ Furthermore, the CCR5/CCL5 axis also plays a critical role in the progression of multiple solid tumors, including gastric cancer (GC),¹⁸² glioblastoma,⁴⁴ head and neck cancer,¹⁸³ lung cancer,¹⁸⁴ ovarian cancer,¹⁸⁵ and so on, often by promoting tumor cell proliferation, metastasis, and assisting in the establishment of immunosuppressive TME.¹⁸⁶

Briefly, the above results suggest that CCL5 and CCR5 are highly expressed in various tumor cells and promote tumor proliferation and metastasis by recruiting immune cells. Based on the finding that CCR5 antibodies retard tumor progression and inhibit angiogenesis,^{179,180} we speculate that CCL5/CCR5 may be a potential target in cancer therapy.

3.2.3 | The CCL5/CCR5 axis in inflammatory diseases

In addition to being involved in the progression of multiple tumors, aberrant CCL5/CCR5 interactions have been identified in multiple types of inflammation,¹⁸⁷ including AD, atherosclerosis, diabetes, hepatitis, and some viral infections.

With the intensive study by scientists of the pathology of atherosclerosis, it is now widely accepted that the disease is an inflammatory disease in which the continuous accumulation of macrophages in the intima and the

rise in cytokine levels in peripheral blood and local tissues are important hallmarks.¹⁸⁸ It has been reported that the chemokine CCL5 assists in the recruitment of monocytes to the intima in the early stages of atherosclerosis and promotes the conversion of macrophages.¹⁸⁹ Recently, Jongstra-Bilen et al.¹⁹⁰ showed that the expression of CCL5 mRNA as well as other ligands of the CCR5 receptor (CCL3 and CCL4) was induced in the aortic intima of Ldlr-/mice 3 weeks after the onset of cholesterol-rich dietinduced hypercholesterolemia. Blockade of CCR5 significantly reduced the recruitment of monocytes at the lesion site, suggesting that CCL5 chemokine signaling through CCR5 is critical. Further, CCL5/CCR5 has been reported to attract T cells to the lesion site to release inflammatory factors (e.g. perforin-1, IL-6, selectin, tumor necrosis factor- α [TNF- α], etc.) and exacerbate inflammatory damage.^{191,192} Besides, CCL5 levels were found to be elevated in damaged tissues of inflammatory bowel disease (IBD), which then induced an influx of inflammatory factors. Knockdown of the CCR5 gene reduced the recruitment and activation of CCR5(+) leukocytes in the mucosa, leading to greatly reduced symptoms of inflammation in a metastatic model of colitis. Similarly, the CCR5 inhibitor maraviroc attenuated the development of intestinal inflammation by selectively reducing the recruitment of CCR5(+) leukocytes.¹⁹³ Upon liver injury, resident Kupffer cells interact with hepatic cell populations and release chemokines to recruit circulating leukocytes, of which monocytes subsequently differentiate into macrophages in the liver, influencing the development of tissue inflammation.¹⁹⁴ It has been shown that the CCL5/CCR5 signaling pathway can accelerate the inflammatory process in the liver through the NF-kB pathway.¹⁹⁵ A new study indicated that CCL5 could directly activate M1 polarization and impede M2 polarization through CCR1- and CCR5-mediated activation of MAPK and NF-*k*B pathways. Neutralizing antibodies or antagonists with CCL5 could greatly reduce liver injury and improve survival in drug-injured mouse models.¹⁹⁶ Additionally, the CCL5/CCR5 axis is also involved in viral infections. COVID-19, a pandemic currently plaguing people worldwide, is caused by SARS-CoV-2 infection. Recent studies have shown that inhibition of the CCL5/CCR5 axis by the monoclonal antibody leronlimab could alleviate the symptoms of patients with critical pneumonia.¹⁹⁷ Also, it was observed that the levels of inflammatory molecules such as CCL5, IL-6, and TNF- α in the serum of patients were reduced after anti-CCR5 treatment.¹⁹⁸

3.2.4 | Clinical trials of drugs targeting the CCL5/CCR5 axis

We have described above the seminal function of the CCL5/CCR5 axis on tumor progression in preclinical

studies, which can be attenuated by knocking down CCL5, using antibody neutralization, and CCR5 antagonists to block ligand-receptor binding, setting the stage for drugs targeting the CCL5/CCR5 axis to enter clinical trials. Table 2 summarizes clinical trials of several CCR5 antagonists (maraviroc, vicriviroc, AZD5672, and leronlimab) for the treatment of metastatic CRC, advanced breast and pancreatic ductal carcinoma, and Kaposi's sarcoma associated with HIV infection (Table 2). In addition, maraviroc has been reported for the treatment of conditions other than tumors, including graft-versus-host disease, hypertriglyceridemia, stroke, and COVID-19 (NCT00948753, NCT01133210, NCT03172026, and NCT04435522). Another dual chemokine receptor antagonist, cenicriviroc, which targets CCR2/CCR5 and inhibits monocyte migration, has also being evaluated for safety and efficacy in clinical trials. Cenicriviroc also inhibits HIV-1 and HIV-2 infection and has potent anti-inflammatory and anti-infective activity.^{199,200} Clinical trials related to cenicriviroc have shown a role in the treatment of COVID-19 (NCT04500418), nonalcoholic steatohepatitis (NCT03517540), primary sclerosing cholangitis (NCT02653625), type 2 diabetes mellitus (NCT02330549), and many other diseases.

3.3 | The CCL19/CCL21/CCR7 axis

3.3.1 | Brief introduction of the CCL19/CCL21/CCR7 axis

Chemokines CCL19 and CCL21 are highly expressed in lymphoid tissues and act upon binding to the same receptor CCR7. In primary lymphoid organs (e.g., thymus), CCR7⁺ thymocytes are subject to CCL19 and CCL21 chemotaxis and move between different tissue sections. In particular, the CCL19/CCL21/CCR7 axis plays an instrumental role in thymocyte differentiation, clonal selection, and negative selection.²⁰¹ Within secondary lymphoid organs (e.g., lymph nodes), CCL19 and CCL21 are continuously secreted by high endothelial veins and fibrous reticulocytes, which bind to CCR7 and then induce lymphocytes in the circulation to enter lymphatic vessels and lymph nodes.²⁰¹ CCR7 is mostly expressed on DCs and T cells for orchestrating immune responses.^{202,203} The role of CCR7 in inducing targeted migration of lymphocytes in immune and inflammatory responses is well recognized. As the predominant class of antigen-presenting cells, DCs can rapidly transform to a mature state upon antigen stimulation and upregulate major histocompatibility complex II and several costimulatory molecules, such as CD80, CD86, and CCR7.²⁰⁴ The elevated levels of CCR7 allow DCs to sense the CCL19/CCL21 concentraMedComm

tion gradient, move toward the highest concentration of this signaling protein, enter the lymph nodes for antigenpresenting and then activate T cells.^{205,206} CCR7 also controls the migration of thymocyte-derived regulatory T cells and effector T cells from sites of inflammation to the second lymphoid organ (SLO) as well as their proper localization.^{207,208} CCR7 expressed on the surface of cancer cells can direct malignant cells from the primary site into the lymphatic system by binding to appropriate signaling proteins, spreading in the body and eventually forming metastases in other tissues, which greatly increases the risk of death for patients.²⁰⁹

3.3.2 | Roles of the CCL19/CCL21/CCR7 axis in cancer progression

Because of the pivotal role of the CCL19/CCL21/CCR7 signaling axis in both antigen presentation and activation of T cell-mediated responses, it has been postulated that increasing the levels of CCL19 and CCL21 within tumors could aid immunotherapy of cancer by enhancing the immune response to tumors. The first of these is to increase CCL19/21 concentration within the TME to sharpen the immune response to tumor. For instance, in mouse lung and colorectal models, intratumoral injection of CCL19 protein directly was shown to result in increased DCs as well as CD4⁺ and CD8⁺ T cells in the TME, promote enhanced secretion of proinflammatory factors, such as chemokines CXCL9 and CXCL10, as well as cytokines IL-12, granulocyte-macrophage colony stimulating factor (GM-CSF), and IFN- γ , and decrease levels of immunosuppressive molecules prostaglandin E2 and transforming growth factor- β (TGF- β); ultimately retarding tumor growth.^{210,211} Similarly, in an orthotopic mouse model of breast cancer, intratumoral administration of CCL21 significantly increased the proportion of T cells, NK cells, and DCs within the tumor, reduced the size of the tumor and extended the survival time of tumor-bearing mice.²¹² Introduction of exogenous genes into tumor cells by recombinant plasmid techniques (e.g., lentiviral transfection) is another way to achieve elevated concentrations of CCL19/CCL21 protein. For example, mouse melanoma and ovarian cancer cells transfected respectively to express mouse CCL19 and then inoculated into C57BL/6 mice, showed significantly slower tumor growth compared with the control group without CCL19 expression.²¹³ In a mouse lung metastasis model, injection of endothelial progenitor cells overexpressing CCL19 by tail vein was able to reduce the number of lung metastatic nodules and prolong the survival of mice.²¹⁴ In addition, transfection of breast cancer MCF-7 cells with CCL21 protein potentiated a range of functions of DCs, such as antigen uptake

and presentation, migration, and antiapoptotic ability in vitro. $^{\rm 215}$

Therapeutic strategies that increase the intratumoral CCL19 or CCL21 levels may also be utilized in combination with other immunotherapies or nonimmunotherapies to improve antitumor efficacy. DNA vaccines have been a particularly attractive approach in recent years to enhance protective antitumor immunity by mobilizing leukocytes (e.g., cytotoxic T cells and NK cells) to the tumor. When combined with CCL21, the DNA vaccine showed higher efficacy than single treatment in a mouse model of orthotopic melanoma.²¹⁶ In addition, MSCs expressing CCL19 have been demonstrated to promote immune cell infiltration into TME and enhance the efficacy of anti-PD-L1 antibodies.²¹⁷ Therefore, targeting the CCL19/CCL21/CCR7 axis to inhibit lymphatic metastasis but maintaining a robust antitumor immune response has increasingly become a bright spot in tumor immunotherapy.²⁰⁹

3.3.3 | The CCL19/CCL21/CCR7 signaling axis in autoimmune diseases

RA is a chronic, systemic autoimmune disease of unknown etiology, characterized by intraarticular inflammatory cell infiltration and elevated proinflammatory cytokines, which can lead to multiple joint deformities and even loss of function.²¹⁸ Page et al.²¹⁹ detected DC subsets within the synovium of RA patients by immunohistochemical staining and showed that immature DCs were found only in the lining layer of the synovium, whereas mature DCs were found in the perivascular lymphatic aggregation zone. In addition, the expression of CCL19, CCL21, and CCR7 was only increased in the perivascular area, suggesting that the expression of these chemokines as well as CCR7 is associated with lymphocyte aggregation. In addition, upregulation of CCL19 and CCR7 gene expression was shown in psoriasis patients, whose key role is involved in establishing the typical inducible skin-associated lymphoid tissue structures during disease progression, which can be clearly identified in the skin aggregates at the lesion site.²²⁰ The majority of lymphocytes in healthy human cerebrospinal fluid (CSF) are CCR7⁺ central memory T cells,²²¹ whereas in patients with relapsed and progressive MS, increased expression of CCL19 is found in CSF,²²² implying that the CCL19/CCR7 axis may be involved in the normal immune surveillance of the brain. In experimental autoimmune encephalomyelitis (EAE) models, blocking CCR7 signaling has been proved to reduce the binding of T cells to inflammatory venues in EAE brain slices.^{223,224} Collectively, these results suggest that the CCL19/CCR7 axis plays an important role in the progression of autoim-

3.3.4 | Clinical trials of drugs targeting the CCL19/CCL21/CCR7 signaling axis

As mentioned above, modulating the function of the CCL19/CCL21/CCR7 axis may hold therapeutic potential for cancer as well as many inflammation-related diseases, and there are several clinical trials currently underway.

One of the phase I trials is studying the side effects and optimal dose of autologous DC-adenovirus CCL21 vaccine combined with intravenous pembrolizumab and seeing how well they work in treating patients with stage IV nonsmall cell lung cancer (NCT03546361). The researchers concluded that vaccines made from genetically modified viruses may help the body build an effective immune response to kill tumor cells, whereas monoclonal antibodies, such as pembrolizumab, may interfere with the ability of tumor cells to grow and spread, so giving a CCL21 genetically modified DC vaccine with pembrolizumab to treat patients with stage IV nonsmall cell lung cancer may work better. This clinical trial enrolled 24 patients, and up to 12 patients will participate in the dose escalation phase, during which 12 patients will be evaluated during the dose expansion. Two additional phase I clinical trials investigated the safety, toxicity and maximum tolerated dose of the autologous DC-adenovirus CCL21 vaccine. The vaccine as an intratumoral injection was well tolerated by patients with advanced or recurrent nonsmall cell lung cancer and cutaneous melanoma (NCT00601094, NCT00798629). Besides, JBH492 is an antibody-drug conjugate that consists of an antibody against CCR7 on tumor cells combined with the steroid DM4, which leads to inhibition of tumor cell proliferation. A phase I/Ib Open-label clinical trial (NCT04240704) is currently undertaken for investigating the preliminary effects of JBH492 monotherapy on non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

3.4 | The CCL20/CCR6 axis

3.4.1 | Major characteristics of the CCL20/CCR6 signaling axis

Since its discovery in the 1990s, CCL20 has gradually been attributed several names, such as MIP- 3α , liver and activation regulatory chemokine and exodus-1, and it has gained increasing attention in molecular and cellular immunology. A very large number of cells in the

body express CCL20, including CD8+ T cells, B lymphocytes, T helper 17 cells, macrophages, neutrophils, DCs, mast cells, and endothelial cells.²²⁵⁻²²⁷ As an inflammatory chemokine, CCL20 strongly attracts lymphocytes and DCs to lymphoid tissues, thus participating in the formation and function of lymphoid tissues at various sites. CCL20 also has a predominant role in innate immunity, being upregulated by transcription factors, such as NF κ B,²²⁸ and induced by the TNF- α and IL-1 β .²²⁹ When the immune system is stimulated by inflammatory substances such as lipopolysaccharide, CCL20 is also quickly upregulated, leading to a prompt accumulation of immune cells in the spleen.²³⁰ Currently, there is only one known receptor for CCL20, namely CCR6.231,232 CCR6 is the hallmark chemokine receptor of immune cells. When CCL20 binds to its receptor CCR6, it not only participates in regulating the immune homeostasis of the body, but also serves to modulate the inflammatory response through the Th17 pathway, playing an essential role in the progression of autoimmune diseases and various malignant tumors.^{59,233,234}

3.4.2 | The CCL20/CCR6 axis in cancer progression

With concerted, extensive efforts, the functional role played by the CCL20/CCR6 axis is gradually being unfolded, particularly in regulating cancer progression and metastasis within the TME. Ding et al.²³⁵ revealed that tissue expression of CCL20 in clinical specimens of hepatocellular carcinoma (HCC) was related to tumor size, differentiation, recurrence, and vascular infiltration, and that high CCL20 expression was associated with worse PFS and OS in patients. In in vitro analysis, CCL20 greatly enhanced the invasive ability of triple-negative breast cancer cell lines by increasing the secretion of matrix metalloproteinase (MMP)-2 and MMP-9; meanwhile, anti-CCL20 antibody by intraperitoneal injection in a mouse breast cancer model could effectively inhibit the occurrence of bone metastases.²³⁶ A study showed that serum CCL20 and IL-17A levels were higher in CRC patients than those in healthy subjects, and the combination of CCL20 and IL-17A signature curve analysis could differentiate CRC patients from healthy volunteers effectively.²³⁷ In a case study of chemotherapy resistance to the FOLFOX regimen, CCL20 secreted by tumor cells was able to facilitate Tregs recruitment into the TME, which enhanced chemoresistance and closely correlated with poorer survival rates.²³⁸ Additionally, IL-4-treated M2-type macrophages highly express CCL20 and the CCL20/CCR6 axis promotes pancreatic cancer proliferation and distant metastasis via inducing epithelialmesenchymal transition (EMT) in vivo.²³⁹ Furthermore,

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CCL20 and/or CCR6 proteins were found to be highly expressed in lung,²⁴⁰ cervical,²⁴¹ gastric,²⁴² ovarian cancer tissues,²⁴³ and renal cell carcinoma,²⁴⁴ facilitating tumor proliferation and directional migration through autocrine or paracrine modes.

3.4.3 | The CCL20/CCR6 axis in autoimmune diseases

Similar to the CCL19/CCL21/CCR7 axis, the CCL20/CCR6 axis serves an essential role in the recruitment of inflammatory cells in the immune response and may contribute to a variety of autoimmune diseases, such as MS, IBD, psoriasis, and RA.²³⁴ A study showed that stimulation of human epithelial cells with Th17 cytokines (IL-17A, IL-22, and TNF- α) was able to induce a remarkable increase in CCL20 and CCR6 levels in their cultures in a doseand time-dependent manner. Similar results were obtained in in vivo tests, where subcutaneous injection of these Th17 cytokines also resulted in increased expression of CCL20 and CCR6, as well as infiltration of mature DCs and CD4⁺ T cells in the skin of mice.^{245,246} In several animal models of psoriasis, the use of anti-TNF- α antibody infliximab,²⁴⁷ anti-CCR6 antibody,²⁴⁸ and the anti-CCL20 antibody,²⁴⁹ respectively, significantly reduced regional infiltration of CCR6+CD4+ T cells and attenuated the inflammatory response in affected skin lesions. Significantly elevated levels of CCL20 were also found in the affected joints of RA patients, followed by a marked increase in CD4+CD45RO+CCR6+ memory T cells in the peripheral circulation of the patients.²⁵⁰ Hirota et al.²⁵¹ found that in an animal model of RA, IL-17-producing Th17 cells predominantly expressed CCR6 and its ligand CCL20. Blockade of proinflammatory cytokines with infliximab or anti-IL-6R antibodies significantly decreased the CCL20 level and Th17 cells migration to the joints.²⁵¹ In the MS mouse model known as EAE, CCR6 and CCL20 expression was found to be upregulated in the spinal cord,²⁵² and CCR6-deficient mice showed a milder development of EAE compared with wild-type mice.²⁵³ CCL20 and CCR6 also play an important contribution to the pathogenesis of IBD by regulating the delicate balance of Th17 and Tregs.^{254,255} Data from these results indicate that the CCL20/CCR6 axis is implicated in the pathogenesis of autoimmune diseases and that antibodies or antagonists to CCR6 or CCL20 hold promise as an intriguing treatment tactic to ameliorate neuroinflammation and autoimmunity.

A human monoclonal antibody (MOR103) to GM-CSF was well tolerated in randomized clinical trials and showed preliminary evidence of efficacy in RA (NCT01023256) but little improvement in the severity of MS (NCT01517282). Additional animal experiments and clinical trials are certainly needed to gain more insight into the pivotal roles of the CCL20/CCR6 axis in human disease.

3.5 | The CXCL5/CXCR2 axis

3.5.1 | Basics of the CXCL5/CXCR2 signaling axis

CXCL5, previously named epithelial neutrophil-activating peptide-78 (ENA-78), is characterized by its ability to recruit neutrophils during the immune response,^{27,256} contribute to angiogenesis and reshape the connective tissue.²⁵⁷ CXCL5 is secreted by cells stimulated by the inflammatory cytokines IL-1 or TNF- α , whereas many immune cells (e.g., macrophages,²⁵⁸ eosinophils²⁵⁹) and nonimmune cells (e.g., mesothelial cells²⁶⁰ and cancerassociated fibroblasts²⁶¹) are also capable of expressing CXCL5. In addition, the secretion of CXCL5 and IL-1 β in TME interferes with the maturation of functional DCs, and CXCL5 expressed in eosinophils inhibits the secretion of IFN- γ .²⁶² CXCL5 activates downstream signaling pathways by binding to the IL-8B receptor, which later became known as CXCR2 and is highly expressed on neutrophils, although CXCR2 also binds to other ligands, including CXCL1-3 and CXCL6-8.2

3.5.2 | The CXCL5/CXCR2 signaling axis in cancer progression

The relationship between the CXCL5/CXCR2 signaling axis and carcinogenesis is increasingly being recognized. Abnormal elevations of CXCL5 and/or CXCR2 proteins have been noted in as many as 14 distinct malignant tumor types, including but not limited to CRC,^{263,264} nonsmall cell lung cancer,²⁶⁵ breast cancer,²⁶⁶ bladder cancer,²⁶⁷ nasopharyngeal carcinoma,²⁶⁸ and so on. The expression intensity of CXCL5 was also detected in line with the malignancy degree, metastasis, and survival of cancer patients, which provides new potential for clinical application.²⁷ The CXCL5/CXCR2 signaling axis can also indirectly promote tumor progression via modulating the function of various immune cells within the TME. For instance, Zhou et al.²⁶⁹ discovered that CXCL5 might contribute to the likelihood of tumor metastasis and recurrence in a mouse intrahepatic cholangiocarcinoma model via recruiting intratumoral neutrophils. Overexpression of CXCL5 on HCC stem cell-like cells recruits immunosuppressive neutrophils and promotes lymphatic metastasis of tumor cells through binding CXCR2.²⁷⁰ MDSCs in breast and renal cell carcinomas were shown to be related to tumor grade and positively correlated with CXCL5 expression.^{271,272}

In addition, a positive correlation was noted between CXCL5 expression and the number of CD8⁺ T cells, CD11b⁺MMP9⁺Ly6G⁺ granulocytes and macrophages in colorectal and pancreatic cancers.^{263,273}

Because of CXCL5's chemotactic effect on vascular endothelium, it is also considered to be a potent angiogenic factor. In animal studies of bladder, renal cell, and CRCs, CXCL5 secreted by tumor cells binds its receptor CXCR2 and activates the downstream AKT/NF-kB signaling pathway, thereby stimulating the proliferation and aggregation of endothelial cells.²⁷⁴⁻²⁷⁶ Data from several sources have identified the involvement of CXCL5 in the proliferation of other types of tumor cells, such as prostate cancer,²⁷⁷ lung cancer,²⁶⁵ cervical cancer,²⁷⁸ hepatoblastoma,²⁷⁹ osteosarcoma,²⁸⁰ and papillary thyroid carcinoma.²⁸¹ In addition, the levels of CXCL5 were significantly higher in the lymph node metastatic tissue of head and neck squamous cell carcinomas than those in the primary tumor area.^{282,283} CXCL5 expression was also stronger in HCC cell lines with high metastatic potential than that in their less aggressive counterparts, due to its ability to strongly activate the ERK1/2 and PI3K/AKT signaling pathways in tumor cells.^{284,285}

3.5.3 | The CXCL5/CXCR2 axis in inflammatory diseases

Due to the strong chemotactic effect of CXCL5 on neutrophils, its role in regulating the inflammatory response has been widely noted. In a study of mechanical pain sensitization caused by ultraviolet B (UVB), Dawes et al.²⁸⁶ explored changes in all chemokines and inflammatory factors in inflamed skin sites in humans and rats after UVB exposure. It was found that CXCL5 expression was most significantly elevated in the inflamed skin. Moreover, CXCL5 injection via the plantar area triggered a dosedependent decrease in mechanical pain threshold in rats, a result that reveals for the first time the mechanism of CXCL5 involvement in chronic inflammatory pain.²⁸⁶ In addition, Xu et al.²⁸⁷ found that the expression of CXCL5 and its receptor CXCR2 was elevated notably in spinal cord neurons of rats with chronic constriction injury of the sciatic nerve, and that the CXCL5/CXCR2 pathway regulated the phosphorylation of glycogen synthase kinase-3 (GSK-3 β), which induced neuropathic pain in rats. Mild inflammation promotes retinal ganglion cell (RGC) survival and axonal regeneration after optic nerve (ON) injury with the involvement of infiltrating macrophages and neutrophils. Interestingly, the expression of Cxcl5 and Cxcr2 is increased when the ON and lens are injured. In retinal graft cultures, the addition of recombinant CXCL5 promoted RGC survival and neurite growth with an increase

in the number of activated microglia, a phenomenon that was inhibited by the CXCR2 antagonist SB225002.²⁸⁸

In pulmonary inflammation, the polymorphonuclear neutrophils (PMNs) recruited from the blood are essential for alveolar space defense and pathogen clearance. However, when PMNs are extensively translocated into the interstitial and alveolar spaces of the lung, they can lead to uncontrolled immune responses.²⁸⁹ CXCR2 is obviously upregulated in airway epithelial cells during acute exacerbations of chronic obstructive pulmonary disease (COPD), and there is a significant positive correlation between CXCR2 expression and the number of neutrophils. Blocking CXCR2 reduced the proportion of neutrophils in bronchoalveolar lavage fluid in a mouse model.²⁹⁰ Asthma is also a chronic inflammatory disease of the lungs, and although the role of neutrophils in stable asthma is unclear, a significant increase is observed in late responses to stimulation or asthma exacerbation, accompanied by increased levels of CXCL5 and CXCR2.291 CXCL5 and its receptor CXCR2 were overexpressed in lung tissue of acute respiratory distress syndrome (ARDS) through the upregulation of MMP-2 and MMP-9.²⁹² In addition, CXCL5-neutralizing antibodies effectively attenuated the inflammatory response, diffused alveolar injury and pulmonary edema, and reduced the expression levels of MMP-2 and MMP-9 in ARDS mouse models.²⁹² Further studies confirmed that CXCR2 is essential for the development of autoantibody-mediated arthritis and that it upregulates the expression of the corresponding ligands CXCL1, CXCL2, and CXCL5.²⁹³⁻²⁹⁵

The results of these studies suggest that blocking CXCL5/CXCR2 signaling appears to be a promising strategy for a wide range of inflammatory diseases and that in-depth studies of this pathway are warranted.

3.5.4 | Therapeutic strategies targeting the CXCL5/CXCR2 axis

In recent years, the CXCL5/CXCR2 axis has received increasing attention for its potential in cancer screening, tumor prognosis and personalized anticancer therapy. First, in vivo tests have shown that blocking CXCL5 or applying CXCR2 antagonists can slow disease progression by blocking the AKT/NF- κ B signaling pathway, thereby effectively reducing the blood supply to the tumor.²⁹⁶ In addition, CXCL5-neutralizing antibody-treated mice showed reduced metastasis of breast cancer cells, mainly through inhibition of ERK/Snail signaling.²⁹⁷ Meanwhile, therapeutic strategies targeting CXCL5/CXCR2 in combination with chemotherapy or immunotherapy have being explored. For example, in a mouse lung cancer model, CXCL5 antibodies synergistically enhanced the therapeu-

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tic effect of the tyrosine kinase inhibitor gefitinib through activating the AKT/NF-*k*B and ERK/RSK1/2 signaling pathways.²⁹⁸ Additionally, the CXCR2 antagonist SCH-527123 not only inhibited tumor proliferation, invasion, and angiogenesis, but also enhanced the sensitivity of CRC to oxaliplatin treatment.²⁹⁶ In a phase I clinical trial of patients with human epidermal growth factor receptor-2 negative metastatic breast cancer, a 30% responsiveness was observed for orally administered noncompetitive CXCR1/2 antagonist reparixin adjuvant to paclitaxel, and there was no pharmacokinetic effect between the two drugs (NCT02001974). Navarixin (MK-7123), a CXCR2/CXCR1 antagonist with oral bioavailability, is currently evaluated in clinical trials for its efficacy and safety in advanced/metastatic solid tumors, psoriasis, and COPD (NCT03473925, NCT00684593, NCT00688467, and NCT01006616). Danirixin, another selective CXCR2 antagonist with high affinity, is able to effectively inhibit the binding of CXCL8 (IL-8) to CXCR2, and several clinical trials have focused on its improvement of lung function in patients with mild to severe COPD (NCT03136380, NCT03250689, NCT03034967, and NCT02130193).

3.6 | The CXCL9, -10, -11/CXCR3 axis

3.6.1 | Introduction to the CXCL9, -10, -11/CXCR3 axis

CXCL9, -10, and -11 are selective ligands of CXCR3. These ligands are primarily produced by cancer cells, endothelial cells, fibroblasts, and monocytes, and are commonly expressed at low levels in the homeostatic state, but are upregulated when stimulated by cytokines, such as TNF- α and IFN- γ .^{299,300} CXCL9, which is referred to as monokine induced by gamma IFN (MIG), primarily mediates lymphocyte infiltration into the lesion site and inhibits tumor growth.³⁰¹ It has been reported that CXCL10, or IFN gamma-inducible protein 10, is intensely induced by IFN- α/β as well as IFN- γ , but weakly induced by TNF- α .³⁰² CXCL11 is considered the predominant CXCR3 agonist due to its stronger potency than CXCL9 or CXCL10, is a major chemoattractant for effector T cells, and stimulates calcium flux and receptor desensitization.³⁰³ CXCR3 is predominantly expressed on CD4⁺ and CD8⁺ T lymphocytes. In the CD4⁺ subpopulation, CXCR3 is abundant on proinflammatory Th1 cells, but was also present on FOXp3+ Tregs.³⁰⁴ It is widely believed that the CXCL9, -10, -11/CXCR3 signaling axis modulates immune cell polarization and activation and directs immune cells toward their focal sites, which include macrophages, cytotoxic lymphocytes (CTL), and NK cells, among others.300,305

3.6.2 | Targeting CXCL9, -10, -11/CXCR3 axis for cancer therapy

Recent studies have reported that CXCR3 expression levels in clinical tumor specimens correlate with metastatic potential and patient prognosis, making it feasible to use the CXCL9, -10, -11/CXCR3 axis as a predictor of treatment outcomes, although the relationship between expression of these three ligands and tumor recurrence or metastasis remains controversial.31,306,307 Using shRNAmediated silencing, Wightman et al.³⁰⁸ determined that CXCL10/CXCR3 coexpression increased tumor cell metastasis and recurrence in both in vitro and in vivo analyses of B16F1 melanoma. Simultaneous reduction of CXCR3, CXCL9, and/or CXCL10 expression suppresses cancer metastasis rates in melanoma,³⁰⁹ CRC,³¹⁰ and breast cancer models.³¹¹ Data from a study on radiotherapy for head and neck cancer showed that circulating lymphocyte populations correlated with serum CXCL10 concentrations, but not with CXCL9.312 Mitsuhashi et al.313 noted that the pretreatment serum concentrations of CXCL10 and CXCL11 in lung cancer patients receiving anti-PD-1 antibodies were significantly correlated with clinical outcomes, and identified tumor-derived CXCL10/11 as a potential circulating biomarker for monitoring drug treatment sensitivity. However, some studies have found a contrary relationship between the expression levels of CXCL9/CXCL10 and poor prognosis, drawing negative conclusion for clinical development.^{314,315}

Drugs that enhance the expression of paracrine CXCL9, -10, and -11 and inactivate CXCR3 expression on cancer cells have exhibited antitumor activity in several tumor models. It has been suggested that blocking PD-1 checkpoint in mouse colon cancer cells (MC38) resulted in increased levels of IFN-y-induced chemokines CXCL9 and CXCL10. In contrast, reducing CXCL9 and CXCL10 expression in animal models significantly decreased the efficacy of anti-PD-1 drugs and limited the aggregation of CD8⁺ T cells within the TME.³¹⁶ In lung and renal cell carcinoma models, intratumoral injection of CXCL9 or CXCL10 proteins, respectively, reduced neovascularization and delayed tumor growth by inducing tumor-infiltrating CXCR3⁺ monocytes.^{317,318} Additionally, a novel CXCL10 fusion protein (IP10-scFv) coadministered with CTLs successfully induced tumor-infiltrating lymphocytes and prolonged survival in mice.³¹⁹ CXCL11 is a controversial target for cancer treatment because it helps induce Tregs migration. In a mouse model of mesothelioma, selective lysing virus transfected with CXCL11 was reported to enhance CTL and NK cell infiltration into TME, but not CD4⁺ T cells.³²⁰ On the contrary, CXCL11 expression was remarkably upregulated in rectal adenocarcinoma, but was not correlated with a better prognosis in cancer patients.³²¹

Pharmacological antagonism of AMG487 against CXCR3 was effective in inhibiting the proliferation of osteosarcoma and colon cancer cells in vitro and attenuated lung metastasis in mouse tumor models.^{322,323}

3.6.3 | Roles of the CXCL9, -10, -11/CXCR3 axis in neurological diseases

It has been shown that CXCR3 and its ligands are expressed at high levels in CSF and peripheral blood of patients with neurological disorders and are potentially useful regulators of neuroinflammatory response.^{324,325} MS is a common chronic inflammatory disease of the CNS characterized by the damage of myelin and oligodendrocytes by inflammatory cells. Early in 1999, Balashov et al.³²⁶ reported that CXCL10 was expressed by astrocytes in MS brain lesions and that CXCR3⁺ T cells were found to be increased in the blood of relapsed/advanced MS patients. However, treatment of rats with EAE with monoclonal antibodies against CXCL10 resulted in an increase in infiltrating CD4⁺ Th1 cells in the CNS and an exacerbation of disease grading in animal models, suggesting that CXCL10 may play a specific inhibitory role in Th1-mediated disease development.³²⁷ In another study, Chung and Liao³²⁸ revealed no significant differences in time to disease onset and severity between CXCR3-deficient (CXCR3^{-/-}) mice and wild-type mice. However, pathological sections revealed more severe and extensive demyelination phenomena and axonal damage in CXCR3^{-/-} mice. Furthermore, in vitro studies indicated that astrocytes respond to infection by upregulating CXCL10 mRNA expression and releasing CXCL10 into the supernatant, which is completely abolished by CXCR3 antagonists.³²⁹ Gliomas account for the majority of CNS tumors, with glioblastoma progression involving glioma stem cells (GSCs) that are refractory to diverse therapeutic options. Shono et al.³³⁰ reported that CXCL10 and CXCR3 were increased in GSCs and a malignant glioma model, celecoxib inhibited the expression of CCL2 and CXCR3 in an NF-*k*B-dependent manner, and in addition, silencing of CCL2 led to a decrease in GSC viability. Sharma et al.³³¹ used high-throughput tissue microarrays to detect CXCR3 and CXCL10 immuno-expression in glioblastoma multiforme (GBM) and diffuse astrocytoma (DA) tissues. Their results showed that among 129 analyzable samples, strong CXCR3 and CXCL10 expression was observed in 72.7 and 50.7% of GBM cases, respectively, whereas CXCR3 and CXCL10 expression in DA cases was 31.8 and 24.5%, respectively. Moreover, CXCR3 antagonist NBI-74330 inhibited the growth of GL261 gliomas and increased the median survival time of CXCR3^{-/-} mice, whereas NBI-74330 did not affect the infiltration of CXCR3+ NK and NKT cells within gliomas, suggesting that CXCR3 may not be a major pathway for NK and NKT cells to enter gliomas.³³² Xia et al.³³³ used tissues from AD patients for immunohistochemistry to demonstrate extensive expression of CXCR3 in brain structures. In addition, they found that CXCL10positive astrocytes were also greatly increased in AD patients compared with controls. Recently, an experiment investigating CXCR3 antagonists in the amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mouse model of AD showed that CXCR3 antagonists increased $A\beta$ phagocytosis in microglia and ameliorated behavioral deficits in diseased mice, suggesting that CXCR3 axis mediates AD-like pathology in APP/PS1 mice and could be a therapeutic candidate for AD.³³⁴

Taken together, the aforementioned studies indicate that targeting the CXCL9, -10, -11/CXCR3 axis may have potential for treatment of both cancers and neurodegeneration.

3.7 | The CXCL12–CXCR4/CXCR7 signaling axis

3.7.1 | Physiological role of the CXCL12–CXCR4/CXCR7 axis

When chemokines bind to their cognate receptors on target cells, they will perform a range of important functions within the tissues. CXCL12, also known as stromal cell-derived factor-1, is the only ligand for CXCR4, which is predominantly secreted by stromal fibroblasts, osteoblasts, and vascular endothelial cells. CXCL12 has been highly conserved during evolution and is one of the most primitive chemokines.³³⁵ By interacting with CXCR4 and ACKR3, CXCL12 is essential for the development of the brain, cardiovascular system, hematopoietic organs, and reproductive cells, and thus the chemokine network of CXCL12/CXCR4/ACKR3 signaling is necessary for life.³³⁶ Studies have shown that CXCL12 secretion is also involved in a range of pathological processes, such as cell damage, heart failure, and inflammation during chemotherapy or after organ irradiation.³³⁶ Increased CXCL12 expression has also been observed in the hypoxic and proangiogenic environment within tumors or during autoimmune diseases.³³⁷ Functioning as a GPCRs, CXCR4 is primarily expressed on the surface of endothelial mature cells, precursor cells, and pericytes.³³⁸ Many factors are implicated in the regulation of CXCR4 expression, including hypoxia, stress, and injury, with HIF-1 α being the most important regulator.³³⁸ Also, CXCR4 expression is influenced by IL-17A released from T cells³³⁹ as well as IL-5, IFN- γ , and TGF- β secreted by stromal cells.³⁴⁰ Although CXCR7 is a member of the GPCR family, it does not induce cellular signaling mediated by G protein subunits (α , β , and γ), its main role is to establish and maintain the gradient of **MedComm**

its ligands CXCL11 and CXCL12 on both sides of the cell membrane.³⁴¹ The process for activating CXCR7 is as follows: CXCR7 binds to the ligand and the CXCR7–ligand complex is subsequently internalized by the cell membrane, a process that leads to the degradation of the ligand while the receptor moves back to the cell membrane.

The CXCL12/CXCR4 signaling axis exerts a regulatory effect on the secretion of cytokines and chemokines, as it is shown to induce the expression of TNF- α , IL-1 α/β , CXCL5, and some other chemokines, but it does not affect the expression of IL-2 or IFN-y.³³⁶ The CXCL12/CXCR4 axis also modulates vascular endothelial adhesion and actin polymerization responses, as well as accommodates the migration of bone MSCs (BMSCs) underneath and beneath leukemic cells.^{342,343} The two receptors CXCR4 and CXCR7 can interact to form a heterodimer, which results in enhanced CXCL12-induced signaling via G proteins. Compared with cells transfected with CXCR4 only, coexpression of CXCR4 and CXCR7 on HEK293 cells resulted in higher calcium flux and more β -arrestin recruitment through activation of downstream ERK signal cascade.^{344,345} The interactions between CXCL12, CXCR4, and CXCR7 display considerable complexity under physiological conditions. When this interaction is disrupted, regulation of this axis can influence the progression of diseases including cancer, CNS, cardiac, and autoimmune diseases.336,346

3.7.2 | The CXCL12–CXCR4/CXCR7 contributes to cancer progression

Numerous studies have explored the role of the CXCL12-CXCR4/CXCR7 axis in various cancer types in recent years.³⁴⁶⁻³⁴⁸ Under the regulation of the CXCL12-CXCR4/CXCR7 signaling axis, cancer tissues can exhibit enhanced cell migration and proliferation by activating signaling cascades within tumor cells, as well as regulate angiogenesis and induce metastasis through the vascular endothelial growth factor (VEGF). Thus, drugs targeting CXCR4 and/or CXCR7 can influence cancer progression pathways by regulating the CXCR4/CXCR7-CXCL12 axis. Several studies have reported that CXCL12 can stimulate the proliferation of various tumor cell lines, including melanoma,³⁴⁹ glioma,³⁵⁰ small cell lung cancer,³⁵¹ gastric cancer,³⁵² pancreatic cancer,³⁵³ and CRC.³⁵⁴ Moreover, CXCL12/CXCR4 regulates EMT in sacral chondrosarcoma,³⁵⁵ oral squamous cell carcinoma,³⁵⁶ and glioblastoma.357 Furthermore, the CXCL12/CXCR4 axis is also critical for tumor cell metastasis and drug resistance in cancer therapy.358-360 Inhibition of the PI3K/AKT/NF-kB signaling pathway by downregulating CXCR4 significantly reduced cell proliferation and

increased apoptosis in osteosarcoma cells.³⁶¹ Notch positively controls CXCL12/CXCR4 function in myeloma cell lines, and in vivo blockade of Notch markedly limits myeloma cell infiltration into bone marrow of mouse xenografts.³⁶² Interference with CXCR4 expression using CXCR4 antagonist or lentivirus shRNA can effectively inhibit tumor cell proliferation and invasion in breast cancer,³⁶³ human hilar cholangiocarcinoma,³⁶⁴ laryngeal squamous carcinoma,³⁶⁵ and esophageal carcinoma.³⁶⁶ Long et al.³⁶⁷ investigated the ability to reduce the proliferation of HEC-1-A cells after inhibiting higher mRNA and protein expression levels of CXCR4 and CXCR7 in endometrial adenocarcinoma by RNA interference. Apart from these findings, immunohistochemistry showed that elevated expression of CXCR7 was related to increased tumor grade of prostate cancer, and its overexpression also increased the release of VEGF and the proinflammatory cytokine IL-8, which might promote the invasiveness of tumor cells.^{368,369} Importantly, enhanced CXCR7 expression was associated with poor prognosis in patients with prostate cancer and glioblastoma, suggesting that CXCR7 may serve as a prognostic biomarker for these two tumors.^{370,371} In an animal model of prostate cancer, coadministration of CCX771 (a CXCR7 inhibitor) and enzalutamide remarkably inhibited tumor growth and macrovascular formation, thus suppressing the drug resistance of enzalutamide.372

3.7.3 | Other diseases involved in CXCL12-CXCR4/CXCR7 regulation

CXCL12 is involved in the release of inflammatory factors during the immune process and may influence the pathogenesis of atherosclerosis and osteoarthritis.^{373,374} CXCL12 from the subchondral layer binds to CXCR4 in chondrocytes and induces articular cartilage degeneration by promoting a shift of TGF- β receptor type I (T β RI) from activin receptor-like kinase 5 (ALK5) to ALK1 in chondrocytes.³⁷³ Gao et al.³⁷⁵ found that CXCL12 interacted with CXCR4 to activate the GSK- $3\beta/\beta$ -catenin/TCF21 pathway, thereby reducing plasma HDL-C levels and the efficacy of reverse cholesterol transport, inhibiting ABCA1dependent cholesterol efflux from macrophages, and exacerbating atherosclerosis. During embryonic development, CXCR7 expression is critical for cardiovascular system function. In vitro studies have shown that CXCL12 induced migration of oligodendrocyte precursor cells and angiogenesis of HUVECs through CXCR4-activated MEK/ERK and PI3K/AKT pathways. Knockdown of CXCR4 could also reverse these phenomena and downregulated the MEK/ERK and PI3K/AKT pathways.^{376,377} Furthermore, CXCR7 also facilitates cardiac remodeling by activating endothelial cell proliferation and angiogenesis.³⁷⁸ The gradient of CXCL12 directs CXCR4-positive neural stem cells to differentiate into neuronal cells, including oligo-dendrocytes, astrocytes, and so on, toward the damaged tissue.³⁷⁹ Similarly, the redistribution of CXCL12 due to the increased expression of CXCR7 at the marginal sites of endothelial cells explains the pathogenesis of MS.³⁸⁰ Several modulators that have entered clinical trials targeting the CXCL12–CXCR4/CXCR7 signaling axis are summarized in Table 2.

3.8 | The CXCL13/CXCR5 axis

3.8.1 | A brief introduction of the CXCL13/CXCR5 axis

Originally known as B cell-inducible chemokine 1 or B lymphocyte chelator, CXCL13 forms a unisexual ligandreceptor pair with CXCR5 that is essential for the homeostatic organization of the B cell compartment of secondary lymphoid tissue. CXCL13 is secreted constitutively by stromal cells (e.g., follicular high endothelial vein cells) in the B-cell region of secondary lymphoid tissues (follicles), thus correctly orchestrating CXCR5⁺ T/B lymphocytes and macrophages from the blood into the follicles.^{381–383} CXCR5 is also named Burkitt's lymphoma receptor 1 because it was initially isolated from Burkitt's lymphoma and its expression is detected on tonsillar B cells as well as in all peripheral blood. Similar to other chemokine receptors, CXCR5 is kinetically modulated on T cells and is upregulated on memory/effector T cells following T cell receptor stimulation, whereas IL-2 causes its downregulation.^{384,385} CXCR5 shares 40% amino acid homology with CXCR1, so when CXCL13 activates CXCR5. this signaling axis can lead to intracellular calcium ion influx and induce the activation of several intracellular signaling cascades, such as PI3K/AKT, MAPK/ERK, and Rac pathways, playing a role in immune disorders as well as tumor progression.^{384,386}

3.8.2 | Roles of the CXCL13/CXCR5 axis in cancer progression

Abnormal activation of CXCL13/CXCR5 signaling has been implicated in the development of several advanced solid cancers as well as hematological malignancies. For instance, expression of CXCL13 and/or CXCR5 correlates significantly with tumorigenesis, and CXCL13 is considered a predictive factor for lung cancer progression and early diagnosis.^{387,388} A recent interesting study focused on the correlation between CXCL13 and patient prognosis in patients with squamous lung cancer receiving corticosteroids and chemotherapy.³⁸⁹ This study determined that perivascular CXCL13-positive niches induced the forming of tertiary lymphoid structures, which was correlated with better patient survival. However, studies also have shown that treatment with steroids compromised the formation of these tertiary lymphoid structures, compared with those who were untreated.³⁸⁹ There is also evidence that CXCL13 secreted by PD-1 high expressing tumor infiltrating CD8+ lymphocytes helps to induce other immune cell subsets into TME, including B lymphocytes and T follicular helper cells (TFH cells). Moreover, CXCL13 and CXCL13+ immune cells in the TME of nonsmall cell lung cancer strongly predicted patients' response to anti-PD-1 therapy, correlating with improved durable response and prolonged OS.³⁹⁰ It seems that there is a strong correlation between the CXCL13/CXCR5 axis and breast cancer progression, which have been verified in several studies. Using microarray analysis, CXCL13 was found to be the most overexpressed chemokine in breast cancer tissues when normal breast tissues were used as controls, while a positive correlation was identified between the expression of CXCL13 and CXCR5.³⁹¹ In addition, expression levels of CXCL13 and CXCR5 could be potential biomarkers for diagnosis and prognosis for breast cancer.^{392–394} Of interest, the results of a recent in vitro study have suggested that an anti-CXCL13 antibody reduced the levels of activated ERK and cyclin D1 and potentiated the cleavage of caspase-9, thereby reducing the viability of MDA-MB-231 breast cancer cells.³⁹⁵ Furthermore, treatment with the anti-CXCL13 antibody inhibited ERK activation and slowed tumor growth in a 4T1 mouse model of breast cancer, thus providing a rationale for clinical trials targeting CXCL13.³⁹⁶ Immunohistochemical analysis of specimens from various tumors (including ovarian cancer,³⁹⁷ CRC,³⁹⁸ prostate cancer,³⁹⁹ melanoma,⁴⁰⁰ clear renal cell carcinoma,⁴⁰¹ and nasopharyngeal carcinoma⁴⁰²) showed that CXCL13 and CXCR5 were markedly elevated in tumors, as compared with normal tissue, and contributed to the ability of tumor cells to proliferate, migrate, and invade, ultimately affecting tumor progression, metastasis, and OS. Elucidating CXCL13/CXCR5 signaling effects and downstream signaling pathways will help investigate the molecular mechanisms that control tumor progression and responses to targeted therapies, accelerating the translation of drug research into clinical precision medicine.

3.8.3 | The CXCL13/CXCR5 axis in autoimmune and infectious diseases

The formation of CXCL13/CXCR5-derived tertiary lymphoid structures has been associated with the evolution of MedComm

a divergent range of diseases, including MS, myasthenia gravis, Sjögren's disease, RA, bullous pemphigoid, Graves thyroiditis, and infectious diseases. We already know that abnormal lymphocyte aggregates develop within the affected synovial membrane in patients with RA, and in fact, intense expression of CXCL13 mRNA and protein was detected in areas of B-lymphocyte aggregation, thus facilitating endothelial progenitor cell homing and angiogenesis during RA progression.⁴⁰³ A similar role of CXCL13 and/or CXCR5 in regulating the formation of ectopic lymphoid structures was subsequently found in myasthenia gravis,⁴⁰⁴ Sjögren's syndrome,⁴⁰⁵ and SLE.⁴⁰⁶ Further, the expression levels of CXCL13 are associated with the progression and unfavorable prognosis of the abovementioned diseases and has been suggested as a biomarker to predict the progression of these diseases. Indeed, the CXCL13/CXCR5 axis not only affects the abnormal activity and differentiation of B cells, but also involves the drive of TFH cells. For example, CXCR5+/CD4+ T cells in circulation were similar to TFH cells and have been noted in SLE patients, and they are also engaged in promoting the differentiation of pathological B cells and are associated with disease progression.407

Before the cloning of CXCL13, CXCR5 was determined to be as a coreceptor required during HIV-2 infection of host cells, rendering TFH cells vulnerable to viral infection. During HIV infection, the expression of CXCL13 and CXCR5 was demonstrated to be dysregulated, for example, as HIV infection progressed, the number of CXCR5+ B lymphocytes decreased, whereas plasma levels of CXCL13 increased.408 Subsequent studies confirmed the elevation of serum CXCL13 levels during chronic HIV infection and demonstrated an association of CXCL13 secretion with both viral load and disease progression.⁴⁰⁸⁻⁴¹⁰ Li et al.⁴¹¹ revealed that in patients with chronic hepatitis B (CHB), CXCR5⁺CD8⁺ T cells were partially depleted but possessed greater antiviral capacity than the CXCR5⁻ subpopulation; furthermore, the CXCL13 from CHB patients promoted the infiltration of intrahepatic CXCR5⁺CD8⁺ T cells, a subpopulation that produces anti-HBV-specific IFN- γ and IL-21 and improves treatment response in CHB patients. Notably, administration of CXCR5⁺CD8⁺ T cells to CHB mice resulted in a significant reduction in HBsAg expression in the same study. Intriguingly, overexpression of CXCL13 was detected in the muscles of monkeys chronically infected with the Lyme disease pathogen Borrelia burgdorferi, but the bacterium did not appear to have an effect on plasma levels of CXCL13 chemokines. In contrast, once B. burgdorferi infected the CNS, constitutively elevated levels of CXCL13 were observed in the CSF, contributing to the formation of ectopic lymphoid tissue within the CNS.⁴¹² Neurosyphilis is often an advanced manifestation of a long-term infection, usually



FIGURE 4 Chemokines/chemokine receptor axis in cancers and inflammatory diseases. Multiple chemokines/chemokine receptor axes play important roles in different tumor types and inflammation-related diseases. Almost all organs of the body are regulated by the chemokines/chemokine receptor axes that predominantly affect the progression of tumors and the immune response during inflammation. Development of drugs targeting chemokines or their receptors is a potential strategy for the treatment of these diseases (the figure was created using biorender.com)

presenting as stroke-like symptoms or chronic meningitis. CXCL13 is also thought to be implicated in infection with *Treponema pallidum* (the causative agent of syphilis), with CXCL13 levels within the CSF of syphilis patients being 100-fold higher than those in uninfected individuals. Pathologically, activation and enrichment of B cells and ectopic germinal centers were observed in the CNS of neurosyphilis patients, suggesting that *T. pallidum* infection leads to overexpression of CXCL13 in the CFS, causing a strong humoral response that promotes destruction of neural tissue.⁴¹³

4 | CONCLUSIONS

The chemokine system is an extraordinarily complex defense entity in the body, consisting of a huge array of interplaying ligands, receptors, and regulatory molecules that are involved in various cellular processes. Among them, chemotaxis of immune cells (especially lymphocytes) is its core biological function, but its impact goes far beyond that. The contribution of the chemokine network in physiopathological processes is enormous, involving organ development, immune surveillance, inflammation, infection, as well as innate and adaptive immune

responses. It has conclusively been shown that the chemokine/chemokine receptor axis has a tumorigenic role in many different cancer models and clinics (Figure 4) and is also involved in immunosuppression and protective TME formation and can serve as prognostic bioindicators for many hematologic tumors as well as solid tumors. Modulation of the expression of chemokines or their homologous receptors on tumor cells or immune cells in TME provides a basis for the exploitation of new drugs for clinical evaluation in cancer immunotherapy. In fact, in addition to its vital role in tumors, almost all inflammatory diseases involve chemokines and their receptors in one way or another. Nevertheless, many unknown aspects of the role of chemokines and chemokine receptors in human disease remain to be unfolded, which necessitates strong efforts in much more basic animal studies as well as clinical researches.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. H. L. wrote the initial manuscript and created the tables and figures. M. W. and X. Z. revised the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data included in this article are available upon request from the corresponding authors.

ETHICS STATEMENT

Not applicable.

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