Multifaceted roles of chemokines in gastric cancer: From tumor microenvironment modulation to therapeutic targeting (Review)

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Abstract. Gastric cancer (GC) is a malignant solid tumor with limited treatment options, particularly for advanced tumor stages. Chimeric antigen receptor (CAR)-T therapy has been successful in treating hematological malignancies; however, its efficacy in solid tumors remains suboptimal due to the complex tumor microenvironment (TME). The TME in GC comprises diverse signaling molecules and cellular components, including fibroblasts, immune cells and stromal proteins; these components can support tumor growth, invasion and immune evasion. In the GC TME, the dynamic interactions between cytokines, chemokines, growth factors and their receptors can foster chronic inflammation and immunosuppression, thereby facilitating tumor progression, metastasis and therapeutic resistance. The present review provides novel insights into the understanding and functional impact of cell-chemokine interaction networks in GC, highlighting the therapeutic implications of chemokines in immunotherapy. In addition, current related research areas are outlined and advances in therapeutic strategies targeting key chemokine signaling pathways are discussed. By providing critical insights into TME reprogramming and immunomodulation, the current study aims to encourage the strategic application of chemokine engineering in next-generation CAR-T immunotherapy for GC.

Contents

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1. Introduction

Gastric cancer (GC) is one of the most common malignancies and the third leading cause of cancer-related mortality worldwide (1-3). The etiology of GC is multifactorial, and is influenced by genetic alterations, dietary practices, lifestyle factors, atrophic gastritis, *Helicobacter pylori* and Epstein-Barr virus (EBV) infections (4,5). Notably, >70% of patients with GC are currently diagnosed at an advanced stage due to the absence of routine screening methods and the asymptomatic nature of early disease. Additionally, this group of patients constitutes a population with a high mortality rate, due to the lack of targeted therapies, resistance to chemoradiotherapy and distant metastases. Therapeutic success rate is high for patients with early-stage gastric cancer, with 5-year survival rates of >90% (6); among patients with advanced-stage disease, the prognosis remains poor, with a 5-year survival rate of 5-10% (7). Therefore, novel effective therapeutic approaches are urgently needed to improve the clinical outcomes of patients with GC.

Immunotherapy has transformed GC research from a purely tumor-centered model into a broader immune-biology framework, greatly advancing the understanding of its molecular characteristics, tumor heterogeneity, immune interactions, molecular subtypes, tumor immune microenvironment, immune escape mechanisms and biomarker discovery, while demonstrating considerable therapeutic potential. Multiple immunotherapies have been designed to activate the immune system and enhance antitumor responses in patients with GC, including immune checkpoint inhibitors (ICIs) [such as nivolumab (8) and pembrolizumab (9)] and antigen-targeted chimeric antigen receptor (CAR)-T cell therapies, which include claudin 18.2 (CLDN18.2), mucin 3A, mesothelin (MSLN) and carcinoembryonic antigen (CEA). Notably, CLDN18.2-targeted therapies, such as the monoclonal antibody zolbetuximab, have demonstrated survival benefits in phase III trials (10,11), and CLDN18.2-targeted CAR-T-cell therapies have shown early but promising efficacy (12). However, the efficacy is notably limited by the immune cell

composition of the tumor microenvironment (TME). As chronic inflammation is a critical component in the development of human GC, the TME in GC presents a highly dynamic and complex ecosystem that comprises diverse extracellular matrix proteins, secretory proteins and cellular components. Cellular components include cancer-associated fibroblasts (CAFs), endothelial cells and immunosuppressive cell populations, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) (13-15). The TME in GC has also been shown to be rich in pro-inflammatory cytokines, chemokines and growth factors; the complex interaction between these factors and receptors influences the growth and progression of GC (16).

Chemokines and their receptors are widely expressed in tumor cells, immune cells and stromal cells within the TME. Chemokines are pivotal in mediating directional cell migration, particularly in leukocytes (for example, CXCL8-CXCR1/CXCR2, CXCL9/10/11-CXCR3, CXCL16-CXCR6 and CX3CL1-CX3CR1) (17-20) and promoting angiogenesis (such as CXCL5/CXCL6-CXCR2 and CXCL12-CXCR7) (21,22). Moreover, some chemokines contribute to carcinogenesis by modulating tumor transformation (for example, CCL19/21-CCR7 and CCL2-CCR2) (23,24), invasion (such as CXCL5-CXCR2) (25) and metastasis (such as CXCL8-CXCR1/2 and CXCL12-CXCR4) (18,26). In GC, a comprehensive understanding of the complex interconnected networks of secretory factors within the TME may help to identify new targets for diagnostic and prognostic assessments, and therapy.

The present review presents a comprehensive analysis of the TME in GC, providing novel insights into the cell-chemokine interaction networks in GC and highlighting the therapeutic implications of chemokines in immunotherapy. In addition, current related research areas and therapeutic advances associated with key chemokine signaling pathways in GC are summarized. Specific attention has been paid to the progress and ongoing challenges of chemokine-targeted CAR-T immunotherapy in modulating the immune landscape of the TME in GC. By providing critical insights into TME reprogramming and immunomodulation, the current review aims to advance the strategic application of chemokine-targeted CAR-T immunotherapy in GC.

2. Role of cellular components within the TME in GC

The TME in GC is a highly dynamic and complex ecosystem (27,28). Single-cell sequencing analyses have revealed that the TME in GC comprises various immune cells, including dendritic cells (DCs), T cells and B cells, as well as cellular components, including epithelial cells (ECs), MDSCs, TAMs, tumor-associated neutrophils and CAFs (29). Tumor cells within the TME secrete a range of soluble factors, including chemokines, cytokines, growth factors and extracellular matrix components; these factors contribute to the establishment of tumor-protective barriers and promote tumor growth, angiogenesis and metastasis (30,31). Similar to the TME in a number of other solid tumors, the TME in GC is immunosuppressive, promoting tumor progression and the emergence of an aggressive phenotype. In the GC TME, cells interact through cytokines and chemokines, as shown in Fig. 1. The immune cells within this TME interact primarily through the secretion of cytokines or chemokines that can be broadly categorized as antitumorigenic [such as IL-12, interferon (IFN)-γ, TNF-α, TNF-related apoptosis-inducing ligand, CCL1, CCL19, CCL21, CXCL10 and CXCL16] or pro-tumorigenic (for example, IL-6, IL-23, IL-10, IL-17, TNF-β, MMP-9, CCL2, CCL5, CCL7, CCL12, CCL17, CCL22, CXCL8, CXCL9, CXCL10 and CXCL12) (32-35).

There are two distinct types of macrophages based on cytokine expression, including M1 and M2. M1 macrophages, activated by IFN-γ and microbial components such as lipopolysaccharide, exhibit potent tumor-killing capacity; this type of macrophage expresses high levels of major histocompatibility complex (MHC) class II molecules and produces pro-inflammatory cytokines, including IFN-γ and TNF-α (36). Conversely, M2 macrophages, which are activated by IL-4, produce immunosuppressive cytokines (such as IL-10), and exhibit poor antigen-presenting capacity and tumoricidal activity (37). Under certain conditions, macrophages are recruited to the TME and polarize into TAMs (M1 or M2). Most TAMs present as M2 macrophages that lack the ability to phagocytose tumor cells and serve a crucial role in tumor initiation, invasion, metastasis and immune evasion (38,39). Furthermore, TAMs are critical for modulating the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 axis and promoting the progression of GC cells, thereby contributing to a poor prognosis in patients.

Based on the immunosuppressive role of M2-type TAM in tumor progression and immune evasion, several antitumor strategies aimed at depleting M2-type TAMs or reprogramming them to M1-type have been developed. One study reported an immunosuppressive M2-like profile in a subset of TAMs expressing folate receptor β (FRβ); this study revealed that preconditioning the TME with FRβ-specific CAR-T cells improved the efficacy of tumor-directed anti-MSLN CAR-T cells (40). Furthermore, Zhang *et al* (41) successfully reversed the immunosuppressive, tumor-supportive state of TAMs by delivering mRNA encoding transcription factors IFN regulatory factor 5 and IKKβ. This strategy could reprogram M2-like TAMs into an M1-like phenotype, inducing antitumor immunity and promoting tumor regression. Overall, promoting polarization to the M1 phenotype within the TME offers a promising therapeutic strategy.

CAFs are a heterogeneous population of activated fibroblasts and a central element of the TME; this population is pivotal in tumor progression and metastasis by promoting the migration of cancer cells, altering the metabolism of epithelial tumor cells, regulating the metabolic flexibility of cancer cells and contributing to the development of therapeutic resistance (42). Moreover, CAFs, are a key constituent of the TME that favor cancer progression via the secretion of molecules, including cytokines (such as IL-6, IL-11 and TGF-β), chemokines (for example, CCL2, CXCL8, CXCL9, CXCL10 and CXCL12) and growth factors (for example, fibroblast growth factor). These molecules can directly activate GC cells and promote aggressive phenotypes. It has been reported that a specific subset of CAFs associated with poor prognosis can recruit macrophages into the TME via the C3-C3AR1 axis, and this interaction may govern the response to immune checkpoint blockade in GC peritoneal metastases (GCPM). In addition, chemokines, such

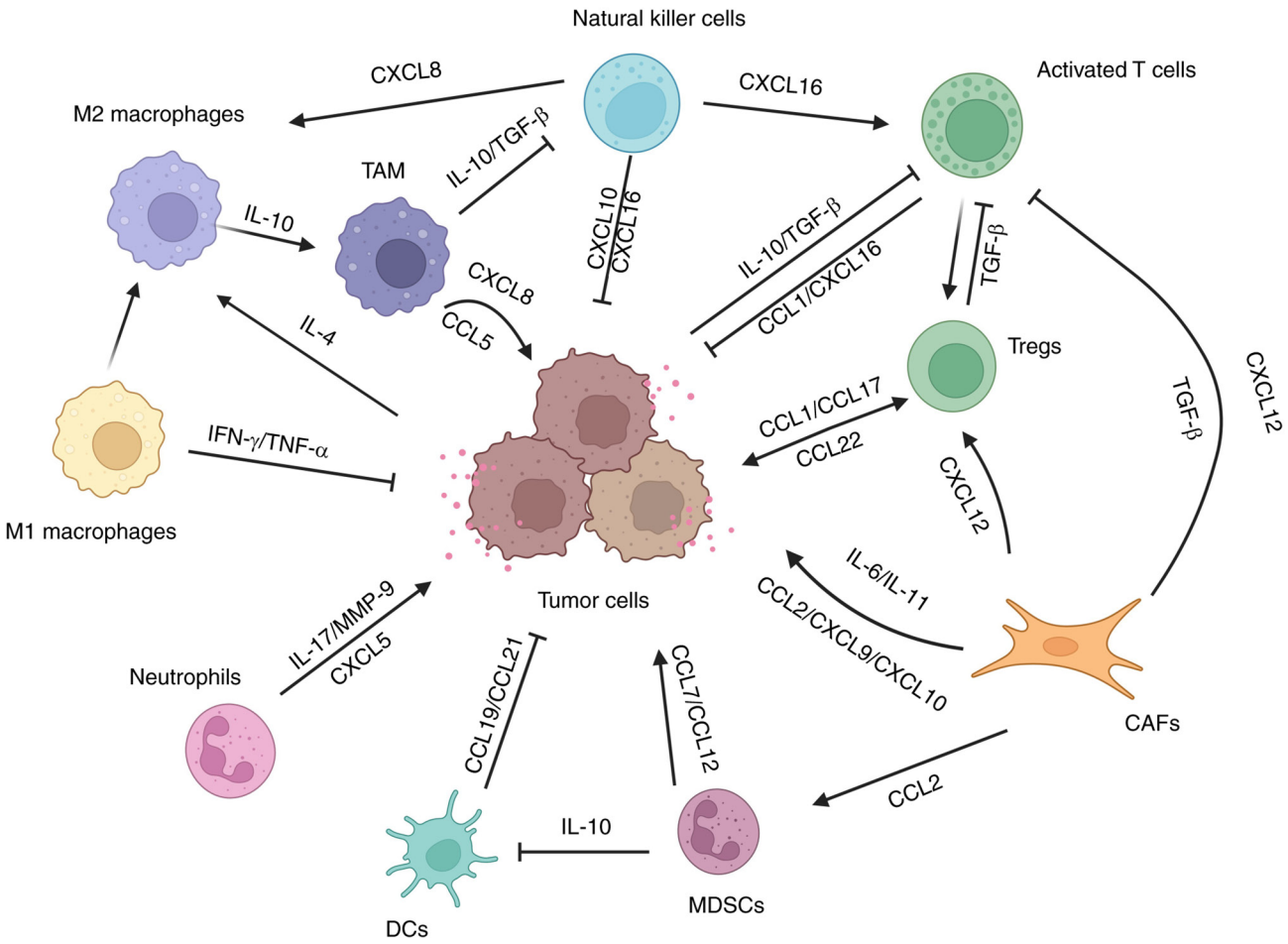

Figure 1. Roles of TAMs, NK cells, DCs, neutrophils, CAFs, cytokines and chemokines in the microenvironment of gastric cancer. TAMs and CAFs promote tumor progression and immunosuppression via CXCL8, CCL5, CXCL12, CCL2 and IL-6/IL-11/TGF-β. Neutrophils secrete IL17, MMP-9 and CXCL5, which are associated with poor prognosis. DC-derived CCL19 and CCL21 promote the migration and orientation of DCs and T cells, and inhibit tumor growth and metastasis; however, CCR7 on cancer cells may reverse this effect. IL-10 secreted by MDSCs inhibits DC maturation. Tumor cells induce T-cell exhaustion via IL-10 and TGF-β and promote tumor growth via CCL1/CCL17/CCL22. CAF, cancer-associated fibroblast; DC, dendritic cell; IFN-γ, interferon-γ; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAM, tumor-associated macrophage; Treg, regulatory T cell.

as CCL2, CCL3, CCL4 and CXCL8, have been demonstrated to exhibit increased expression during GCPM progression; these chemokines facilitate the establishment of an immunosuppressive microenvironment by recruiting inflammatory monocytes, neutrophils and TAM-like macrophages into the peritoneum. The recruited TAM-like macrophages secrete TGF-β, which induces the conversion of peritoneal mesothelial cells into CAFs, thus promoting the formation of pre-metastatic niche (43). Notably, CCR2-positive GC cell subsets have been observed to possess the ability to directly sense the CCL2 gradient on the peritoneal surface and migrate directionally toward higher chemokine concentrations, achieving directed colonization (44). Research has also reported an elevation of pro-inflammatory cytokines (such as IL-6 and TNF-α) in the TME, which can activate the STAT3 pathway in GC cells, and further enhance cell adhesion, survival and implantation on the peritoneal surface (45).

Another study showed that CAFs can suppress the proliferation and migration of $CD8^+$ cytotoxic T cells into tumors partly driven by the secretion of immunomodulatory factors, such as TGF-β and chemokines (46). Moreover, CAFs have been observed to attract, support the accumulation and promote the survival of $FOXP3^+$ Tregs in various types of cancer (47). It has also been reported that CAFs recruit MDSCs into the TME via CCL2 release, thereby suppressing $CD8^+$ T-cell proliferation and IFN-γ production (48). These coordinated effects establish a profoundly immunosuppressive TME.

Fibroblast activation proteins (FAPs) are membrane-bound serine post-prolyl peptidases with endopeptidase activity, which are expressed on CAF subsets in various tumors and represent a promising therapeutic target. Fang *et al* (49) developed a monoclonal antibody linked to a tubulin-binding maytansinoid and a bispecific antibody that could target FAP on CAFs and death receptor 5 simultaneously, which demonstrated potent antitumor activity. Another study revealed that FAP-targeting CAR-T cells can enhance the efficacy of CLDN18.2-targeting CAR-T therapy by remodeling the TME (50). Collectively, CAFs are a critical barrier to antitumor immunity.

Lymphocytes, including T and B cells originating from bone marrow progenitors, serve a pivotal role in the immune landscape of GC. They can exert antitumor immune responses and contribute to immune tolerance within the TME, a functional outcome influenced by their specific lymphocyte subset and the signals they receive (51). T cells are primarily

categorized into two types based on their T-cell receptor (TCR) type: αβ-T cells and γδ-T cells. The αβ-T-cell population can be subdivided into $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells. The former can recognize antigens presented by MHC class I molecules, whereas the latter can interact with antigens presented by MHC class II molecules (52).

Tregs in the TME are pivotal in maintaining systemic immune tolerance. In healthy individuals, Tregs in the thymus migrate to peripheral tissues, and actively regulate the activation and proliferation of potentially auto-reactive T cells. This modulation is essential for maintaining immune homeostasis and preventing autoimmune diseases (16).

Dysfunctional T cells and Tregs in the TME are among the most extensively studied immune cell populations. Research has shown that a subset of these cells co-expresses the inducible T-cell co-stimulator and IL-1 receptor 1, which dominate the immunosuppressive process in the TME (53). In addition, expression of immuno-inhibitory molecules, such as PD-1 and cytotoxic T-lymphocyte-associated antigen 4, which are the key targets of various immunotherapies, have been observed on these cells. It has been reported that tumor cells also contribute to immunosuppression by secreting anti-inflammatory cytokines, including IL-10 and TGF-β; the increase in anti-inflammatory cytokines promotes the expansion of Tregs and the production of FAS ligands, in turn inducing the apoptosis of activated T cells (54,55).

Notably, an association between intratumoral $CD8^+$ T-cell infiltration and survival has been detected in patients with GC. A meta-analysis of GC demonstrated that an increase in both intratumoral $CD8^+$ and $CD4^+$ T-cell infiltration is associated with improved overall survival in patients (56). Another meta-analysis has revealed the possibility of immunosuppression and worsening of GC prognosis in the presence of Tregs in the TME. However, no conclusive association between $FOXP3^+$ Treg infiltration and patient outcomes has been observed (57). Based on current solid tumor research, $CD8^+$ T cells are critical for achieving successful treatment outcomes, and it is essential to advocate strategies that can enhance $CD8^+$ T-cell infiltration and promote their persistence in the TME.

3. Role of chemokines and therapeutic implications in GC

Chemokines are a large family of structurally related cytokines, with >40 individual members and their receptors found in humans. Notably, chemokines are a class of small signaling proteins that are important for embryogenesis, hematopoiesis, mitogenicity, and innate and adaptive immunity. Based on the number and location of N-terminal cysteine residues, chemokines are divided into four families: CXC, CC, XC and CX3C (58,59). CCL1-28, a member of the CCL family, exerts chemotactic effects on monocytes, macrophages, lymphocytes and granulocytes. CXCL1-16, which belongs to the CXCL family, is associated with cell differentiation, migration and tumor growth (60). CXC chemokines containing a glutamic acid-leucine-arginine motif (ELR^+) at the C-terminus are considered pro-angiogenic (such as CXCL6 and CXCL8); conversely, those without the ELR motif are anti-angiogenic (for example, CXCL4/9/10) (61). XCL1 and XCL2 belong to the XCL family, and are both involved in the modulation of various immune cells. Notably, XCL1 is primarily expressed in activated T cells, natural killer (NK) cells and NKT cells, whereas XCL2 is predominantly expressed in activated T cells and DCs (62). CX3CL1 from the CX3CL family mediates the adhesion and chemotaxis of mature T lymphocytes, macrophages and DCs by binding to the receptor CX3CR1 (63).

Chemokine receptor-ligand interactions are important for mediating endogenous immune cell trafficking and have been considered as a therapeutic target in immunotherapy for certain types of cancer. Clinical studies of chemokine-based therapies for malignant tumors are currently underway (Table I), highlighting chemokines as promising therapeutic targets. In addition, CAR-T cells engineered to express chemokine receptors have been proven to possess enhanced tumor trafficking and homing abilities. Animal experiments have shown that the co-expression of chemokine receptors (CCR2b, CCR8, CXCR2 and CXCR6) in CAR-T cells targeting GD2, MSLN or B7H3 enhances tumor infiltration and antitumor effects (64-67). In the current review, chemokines that are markedly expressed in GC are summarized. Furthermore, their roles in the TME and related immunotherapies are described, with the aim of providing novel insights into GC immunotherapy.

Effect of the CCL19/21-CCR7 axis on TME. CCL19 is produced by mature DCs, stromal cells in the thymus and the T-cell region of secondary lymphoid tissues. Upregulation of CCL19 induces morphological changes in DCs, promotes T-cell development in the thymus and inhibits DC apoptosis (68). CCL21, mainly expressed by endothelial venules in the lymph nodes and spleen, is related to mature DCs, B cells, T cells and NK cells. The CCL21/CCR7 axis serves a central role in coordinating the encounter between mature DCs and naïve T cells to initiate a pathogen- or tumor antigen-specific T cell-mediated immune response (69).

CCL19 or CCL21 binding to chemokine receptors, such as CCR7, activates various signaling pathways, including the G protein-coupled receptor (GPCR), PI3K and MAPK signaling pathways (70). Upon activation, these pathways regulate cell cytoskeleton remodeling, release of calcium ions and expression of cell adhesion molecules, facilitating cell migration towards areas with a high concentration of chemokines.

The CCL19/21-CCR7 axis exhibits dual roles in tumor progression; its antitumor effects are mediated through the recruitment of CCR7-expressing DCs into the TME, thereby initiating a potent antitumor immune response. By contrast, when CCR7 is overexpressed on the surface of certain cancer cells (such as breast and melanoma cells), the axis exerts a pro-tumorigenic effect (71). Under certain conditions, such as hypoxia, CCR7 expression on cancer cells displays an increasing trend, which upregulates VEGF-C/D expression and in turn promotes lymphangiogenesis. Additionally, multiple inhibitors targeting CCL19 and CCL21, including small-molecule compounds and antibodies, have been developed, some of which have undergone clinical trials. For example, CCX872, a dual inhibitor of CCL2/CCR2 and CCL19/CCR7, has shown efficacy in cancer treatment (72).

In addition to its direct effects on cancer cells, the CCL19/21-CCR7 axis regulates the cellular composition of the TME. Research has shown that increased CCL19 and CCL21 expression favors the infiltration of

Table I. Clinical trials of chemokine-based therapies in cancer treatment.

Chemokine-based therapeutic	Cancer type	Clinical trial ID	Status	(Ref.) or Clinical Trials.gov ID
A, CCL19				
GPC3-CAR-T-CCL19	Hepatocellular carcinoma or squamous cell lung cancer	NCT03198546	Phase I	(76)
CD19-CAR-T-CCL19	Refractory/relapsed B-cell lymphoma	NCT03929107	Phase II	NCT03929107
B, CCL21				
Vaccination	Lung cancer	NCT01433172	Phase I/II	NCT01433172
C, CXCR2				
Transduced tumor-infiltrating lymphocytes	Metastatic melanoma	NCT01740557	Phase I/II	NCT01740557
CXCR2 antagonist (AZD5069)	Metastatic castration-resistant prostate cancer	NCT03177187	Phase I/II	NCT03177187
CXCR2 antagonist (AZD5069)	Head and neck squamous cell carcinoma	NCT02499328	Phase Ib/II	NCT02499328
CXCR2 antagonist (AZD5069)	Pancreatic ductal carcinoma	NCT02583477	Phase Ib/II	NCT02583477
CXCR1/2 inhibitor (reparixin)	Metastatic triple-negative breast cancer	NCT02370238	Phase II	(135)
CXCR1/2 inhibitor (Reparixin)	Early breast cancer	NCT01861054	Phase II	(136)
CXCR1/2 inhibitor (SX-682)	Stage III and IV melanoma	NCT03161431	Phase I	NCT03161431
D, CXCR4				
CXCR4 antagonist (X4P-001)	Advanced melanoma	NCT02823405	Phase Ib	(107)
CXCR4 antagonist (LY2510924)	Solid tumors	NCT02737072	Phase I	NCT02737072
Anti-CXCR4 mAb (BMS-936564)	Relapsed/refractory multiple myeloma	NCT01359657	Phase Ib	NCT01359657
CXCR4 antagonist (BL-8040)	Pancreatic adenocarcinoma	NCT04543071	Phase II	NCT04543071
CXCR4 antagonist (BKT-140)	Multiple myeloma	NCT01010880	Phase I/IIA	NCT01010880
CXCR4 antagonist (plerixafor)	Metastatic pancreatic cancer	NCT04177810	Phase II	NCT04177810
E, CXCR5				
EGFR-CAR-T-CXCR5	Non-small cell lung cancer	NCT04153799	Phase I	NCT04153799
EGFR-CAR-T-CXCR5	Non-small cell lung cancer	NCT05060796	Phase I	NCT05060796

Table I. Continued.

Chemokine-based therapeutic	Cancer type	Clinical trial ID	Status	(Ref.) or Clinical Trials.gov ID
F, CCR2				
CCR2 antagonist (PF-04136309)	Advanced pancreatic ductal adenocarcinoma	NCT01413022	Phase Ib/II	NCT01413022
CCR2 antagonist (PF-04136309)	Metastatic pancreatic ductal adenocarcinoma	NCT02732938	Phase Ib/II	NCT02732938
CCR2 antagonist (CCX872-B)	Pancreatic adenocarcinoma	NCT02345408	Phase Ib	NCT02345408
G, CCL2				
Anti-CCL2 mab (CNTO 888)	Prostate cancer	NCT00992186	Phase II	(137)
Anti-CCL2 mab (CNTO 888)	Solid tumors	NCT00537368	Phase I	NCT00537368
H, CCR4				
Anti-CCR4 mab (KW-0761)	Cutaneous T-cell lymphoma	NCT01728805	Phase III	NCT01728805
Anti-CCR4 mab (KW-0761)	T-cell leukemia-lymphoma	NCT00920790	Phase II	NCT00920790
Anti-CCR4 mab (KW-0761)	Advanced and/or metastatic solid tumors	NCT02281409	Phase I/II	NCT02281409
Anti-CCR4 mab (KW-0761)	Advanced or metastatic solid tumors	NCT02476123	Phase I	NCT02476123
CCR4-CAR-T	Non-Hodgkin lymphoma	NCT07055477	Phase I	NCT07055477
CD30-CAR-T-CCR4	$CD30^+$ Hodgkin and cutaneous T-cell lymphoma	NCT03602157	Phase I	NCT03602157
I, CCR5				
CCR5-targeting leronlimab	Metastatic colorectal cancer	NCT06699836	Phase II	NCT06699836
CCR5 antagonist (vicriviroc)	Colorectal cancer	NCT03631407	Phase II	NCT03631407

CAR, chimeric antigen receptor; GPC3, glypican-3; mAb, monoclonal antibody.

tumor-infiltrating lymphocytes, subsequently improving the prognosis of patients with numerous types of cancer (73). It has also been reported that co-expression of CCL21 or CCL19 on CAR-T cells may promote cell proliferation in solid tumors (74,75). In a clinical trial (NCT03198546), CCL19-engineered glypican-3 CAR-T cells were shown to possess enhanced tumor homing and antitumor activities (76). The CCL19/21-CCR7 axis also demonstrates strong antitumor efficacy in GC. For example, CAR-T cells targeting NK group 2D (NKG2D), and co-expressing CCL19 and IL-15 have been shown to markedly enhance intratumoral T-cell infiltration and expansion in GC (77). Co-expression of CCL21 or CCL19 may recruit DCs, thereby reinforcing the interaction between DCs and T cells, and potentially enhancing the expression of tumor-specific TCR; this may promote a highly effective antitumor response.

Effects of the CXCL8-CXCR1/2 axis on the TME. CXCL8 is also known as IL-8, is secreted by diverse cell types (including monocytes, macrophages, fibroblasts, hepatocytes, ECs and endothelial cells), and recruits and activates neutrophils and granulocytes. CXCL8 binds to two GPCRs, CXCR1 and

CXCR2 (78), both of which are predominantly expressed on leukocytes, but can be also detected on endothelial cells and cancer cells.

CXCL8 is recognized as one of the key chemokines involved in *H. pylori*-induced chronic gastric inflammation, and *H. pylori* and EBV are established major risk factors for GC development (79). Upon *H. pylori* infection, CXCL8 expression in gastric ECs shows an increasing trend. This change promotes the recruitment of inflammatory cells and sustains a chronic inflammatory microenvironment. Persistent inflammation drives the continuous release of mediators; cytokines such as IL-6 and TNF-α activate NF-κB and STAT3, forming a key molecular link between inflammation and carcinogenesis (80).

These activities induce epithelial-mesenchymal transition (EMT), which facilitates tumor initiation. Research has revealed that CXCL5 promotes EMT via CXCR2-mediated activation of the ERK pathway. Furthermore, inflammatory signals activate fibroblasts, promoting their differentiation into CAFs. The CXCL8-CXCR1/2 axis further recruits neutrophils, enhances angiogenesis and favors tumor growth. In addition, CCL2 recruits monocytes and MDSCs, which can differentiate into TAMs and secrete IL-10, establishing an immunosuppressive microenvironment that promotes tumor progression (81,82).

The CXCL8-CXCR1/2 signaling axis, in concert with CAFs, the microbiome and other immune components, serves a critical role in the recruitment of granulocytes (for example, neutrophils and MDSCs) to the TME (83). Inhibition of this axis holds notable therapeutic potential. For example, Ginestier *et al* (84) demonstrated that the combination of docetaxel and repertaxin (a CXCR1/2 inhibitor) was more effective than either agent alone in reducing tumor size in mice transplanted with human breast cancer cells. Another study suggested that existing HER2-targeted therapies combined with CXCR1/2 inhibitors could be an effective strategy to suppress cancer stem-like cell activity, subsequently improving the survival of HER2-positive breast cancer patients (85). Research on GC has also reported that CXCR1/2 inhibitors exhibit similar antitumor effects in GC and effectively suppress malignant tumor growth (86).

A number of researchers have worked on the role of chemokines to address the challenges associated with CAR-T-cell therapy for solid tumors, including tumor heterogeneity, the immunosuppressive microenvironment, and inadequate intratumoral T-cell trafficking and persistence (87). A study in pre-clinical models of aggressive tumors (such as glioblastoma, ovarian cancer and pancreatic cancer) revealed that CAR-T cells modified with CXCR1 or CXCR2 markedly enhance intratumoral T-cell trafficking and persistence, leading to complete tumor regression and durable immunological memory (88). Although the findings are primarily derived from non-gastric malignancies, it also provides important mechanistic insights that may be applicable to GC, a type of malignancy with inadequate T-cell infiltration and an immunosuppressive TME that remain major barriers to effective immunotherapy. Nevertheless, it may hold translational potential in GC treatment given the critical role of CXCL8 in the TME of GC.

Effect of the CXCL9/10/11-CXCR3 axis on the TME. CXCR3 is a chemokine receptor prominently expressed on cytotoxic lymphocytes (CTLs), NK cells, NKT cells, DCs and B cells. CXCR3 directs the trafficking of theses immune cells to specific tissue sites by binding to its cognate ligands: CXCL9, CXCL10 and CXCL11. Notably, the CXCL10-CXCR3 signaling axis serves a particularly critical role in promoting T-cell infiltration into the tumor TME and enhancing the efficacy of cancer immunotherapy (89). Lim *et al* (90) observed that intratumoral injection of DC cells engineered to express CXCL9/10 markedly enhanced intratumoral T-cell infiltration and activity. In this context, the CXCL9/10/11-CXCR3 axis serves a central role in immune cell recruitment to the tumor.

CXCL10 binding to CXCR3 activates multiple downstream signaling pathways, including the JAK/STAT, MAPK/ERK and PI3K/Akt pathways. STAT1 is generally associated with antitumor immune responses, such as enhanced antigen presentation and CTL recruitment. STAT3 is more commonly linked to tumor cell survival, angiogenesis and immunosuppression, highlighting a strong context-dependent effect. Activated ERK and PI3K/Akt signaling pathways, on the one hand, promote tumor cell proliferation and survival, and on the other hand, strengthen antitumor immunity by facilitating the recruitment and activation of T cells and NK cells in immune cells (91,92).

The functional outcomes of CXCL10 signaling are further influenced by tumor type and the status of key molecular pathways. For example, in tumors with strong IFN signaling (such as melanoma and renal cell carcinoma), CXCL10 tends to enhance T-cell activation and exert anti-angiogenic effects through STAT1 and ERK activation, thereby improving responses to immunotherapy. Conversely, in pancreatic cancer, colorectal cancer and glioblastoma, CXCL10 may preferentially activate STAT3 or PI3K/Akt pathways, contributing to immunosuppression and tumor progression. The intricacy of CXCL10-mediated pathways is further intensified by pivotal oncogenic mechanisms, namely the p53 and NF-κB pathways. When p53 function is intact in tumors, DNA damage responses can be enhanced by CXCL10 and tumor cell sensitivity to chemotherapy can be increased, promoting tumor cell apoptosis and improving therapeutic efficacy. However, in p53-deficient tumors, CXCL10 may promote tumor cell survival and drug resistance via activation of the PI3K/Akt pathway (92,93). In GC, p53 is frequently inactivated by TP53 mutations, resulting in either mutant protein accumulation or loss of expression (depending on the mutation type), thereby affecting downstream signaling and CXCL10-mediated effects (94). Moreover, there is a bidirectional regulatory relationship between CXCL10 and NF-κB, which facilitates the formation of a positive feedback loop that amplifies inflammatory signaling and exacerbates immunosuppression within the TME of various types of cancer, such as hepatocellular carcinoma and GC (95).

The CXCL10-CXCR3 axis also holds notable therapeutic potential. It is evidenced that the CXCL10-CXCR3 axis forms a positive feedback loop with IFN-γ, which can enhance cytotoxic T-cell function. Clinical trials have revealed that the persistence of $CXCR3^+$ T cells contributes to durable remission in patients receiving CAR-T therapy (96,97). One study revealed that intratumoral delivery of CXCL10 via an

adenoviral vector could promote the infiltration of $CXCR3^+$ T cells, effectively converting 'cold' tumors into 'hot; tumors and thereby enhancing the efficacy of anti-PD-1 therapy (98). Moreover, CLDN18.2 CAR-T cells engineered to express CXCL10 and IL-15 have been observed to markedly inhibit tumor growth and prolong survival in GC models (99).

The CXCL10/CXCR3 axis exerts complex and bidirectional regulatory effects in cancer, with its function highly dependent on tumor type, signaling context and the characteristics of the TME. Future therapeutic strategies targeting this axis, therefore, should aim to maximize its antitumorigenic activity while minimizing its pro-tumorigenic and immunosuppressive effects.

Effect of the CXCL12-CXCR4 axis on TME. Within the TME of solid tumors, CXCL12 is primarily expressed on tumor-associated lymphatic endothelial cells, TAMs, immature monocytes, blood endothelial cells, ECs, fibroblasts and immune cells (100). CXCR4 serves as a receptor for CXCL12, and CXCL12 binding to CXCR4 activates multiple downstream signaling pathways (including PI3K, Ras, SAPK/JNK, PLC/MAPK, p38 MAPK and Akt), promoting chemotaxis, adhesion and migration, cell proliferation and survival (101).

In GC, the CXCL12-CXCR4 axis is a key driver of locoregional lymph node metastasis. Prior studies have revealed that both CXCL12 and CXCR4 exhibit increased expression in metastatic lymph node tissues compared with in primary tumors (26,102). Another study showed that CXCR4 expression in gastric ECs increases proportionally with advanced Tumor-Node-Metastasis stages, and increased intratumoral CXCR4 expression is associated with a ~30% reduction in 5-year overall survival in clinical practice (103). These findings highlight the prognostic significance of CXCR4. It has been evidenced that CAFs exert an immunosuppressive function in solid tumors, which is critically regulated by chemokines such as CXCL12. Specifically, CAFs mediate immunosuppression by producing CXCL12, which binds to cancer cells and contributes to the exclusion of T cells (104). Steele *et al* (105) demonstrated that tumor-associated lymphatic vasculature directed T-cell egress from tumors via CXCL12 signaling, and that intratumoral antigen encounter modulated CXCR4 expression by effector $CD8^+$ T cells. These findings highlight the role of the CXCL12-CXCR4 axis in regulating T-cell trafficking within the TME, with potential relevance to GC.

The CXCL12-CXCR4 axis, therefore, represents an effective therapeutic target that could contribute to enhancing tumor control, and potentiate the efficacy of chemotherapy or immunotherapy. Multiple agents, such as the monoclonal antibody BMS-936564/MDX-1338, have been developed to specifically target human CXCR4 (106). Mavorixafor, an orally bioavailable CXCR4 antagonist, has been evaluated in a biomarker-driven phase I clinical trial (NCT02823405) regarding its effects on immune cell profiles within the TME. The combination of CXCR4-targeting agents and adoptive cell therapies has emerged as a novel and effective strategy to enhance antitumor efficacy (107). Pre-clinical studies have shown that CXCR4-engineered CAR-based therapies contribute to enhanced T-cell trafficking and improved antitumor efficacy (108-110). Although these findings are primarily derived from non-GC models, CXCL12-CXCR4 signaling may exert a similar effect on T-cell trafficking in GC; however, this warrants further investigation.

Effect of the CXCL16-CXCR6 axis on the TME. CXCL16 exists in both transmembrane and soluble forms; the former functions as an adhesive molecule, whereas the latter acts as a chemoattractant. CXCL16 is expressed by ECs, endothelial cells and immune cells, such as DCs (111). In some contexts, loss of CXCL16 expression is associated with greater aggressiveness in advanced breast cancer, suggesting its role as a tumor suppressor; by contrast, CXCL16 is recognized as an oncogene in other types of cancers *in vivo*, with its upregulation reported in GC, prostate, pancreatic, ovarian and colorectal cancer (112,113). Taken together, the function of chemokines may vary across different tumor types and contexts. In GC, CXCL16 may exhibit context-dependent roles, which warrants further investigation.

CXCR6 is the sole known receptor for CXCL16. CXCR6 encodes a 39-kDa protein and is selectively expressed by memory/effector T lymphocytes, NK cells, NKT lymphocytes and plasma cells (114). Notably, CXCR6 is the most highly and specifically expressed chemokine receptor on tumor-infiltrating CTLs within tumors (115), which is critical for their accumulation and antitumor function.

Wang *et al* (116) used single-cell RNA sequencing, bulk transcriptomics and multiparametric cytometry to map CXC6 expression and found that CXCR6 expression was restricted to intratumoral $CD8^+$ T cells and its induction required the intact tumor tissue microenvironment. These findings suggest that elevated CXCR6 expression within tumors is not primarily driven by CXCL16/CXCR6 ligand-receptor chemotaxis or tumor antigen-specific ligands but rather induced by the tumor tissue microenvironment itself. Di Pilato *et al* (117) revealed an interaction between the CXCR6 expressed on T cells and the CXCL16 expressed on the subset of intratumoral DCs termed DC3s. These DC3s are characterized by co-expression of IL-12b, Fascin1 and CCR7. Notably, DC3s express and trans-present the survival cytokine IL-15, providing critical signals for the local maintenance and proliferation of effector T cells in the TME. Lesch *et al* (118) demonstrated that CAR-T cells engineered to express CXCR6 exhibited enhanced abilities to target and eliminate pancreatic cancer cells, which improved the efficacy of adoptive cell therapy. Pancreatic cancer and GC share immunosuppressive, stroma-rich microenvironments with poor T-cell infiltration, although their immune contexts differ. In this context, strategies that are effective against pancreatic cancer, such as CXCR6 engineering, may also have therapeutic potential for GC, pending further validation. Collectively, CXCR6 may serve as a promising molecular 'guide' to help to improve the infiltration of CAR-T cells into tumors.

4. Further perspectives of chemokine-targeting strategies combined with CAR-T-cell therapy

CAR-T-cell therapy has demonstrated considerable efficacy in eliminating GC cells; however, its application in solid tumors remains limited by the immunosuppression and immune evasion within the TME. Chemokine-based strategies, by which the immune profile within the TME can be regulated,

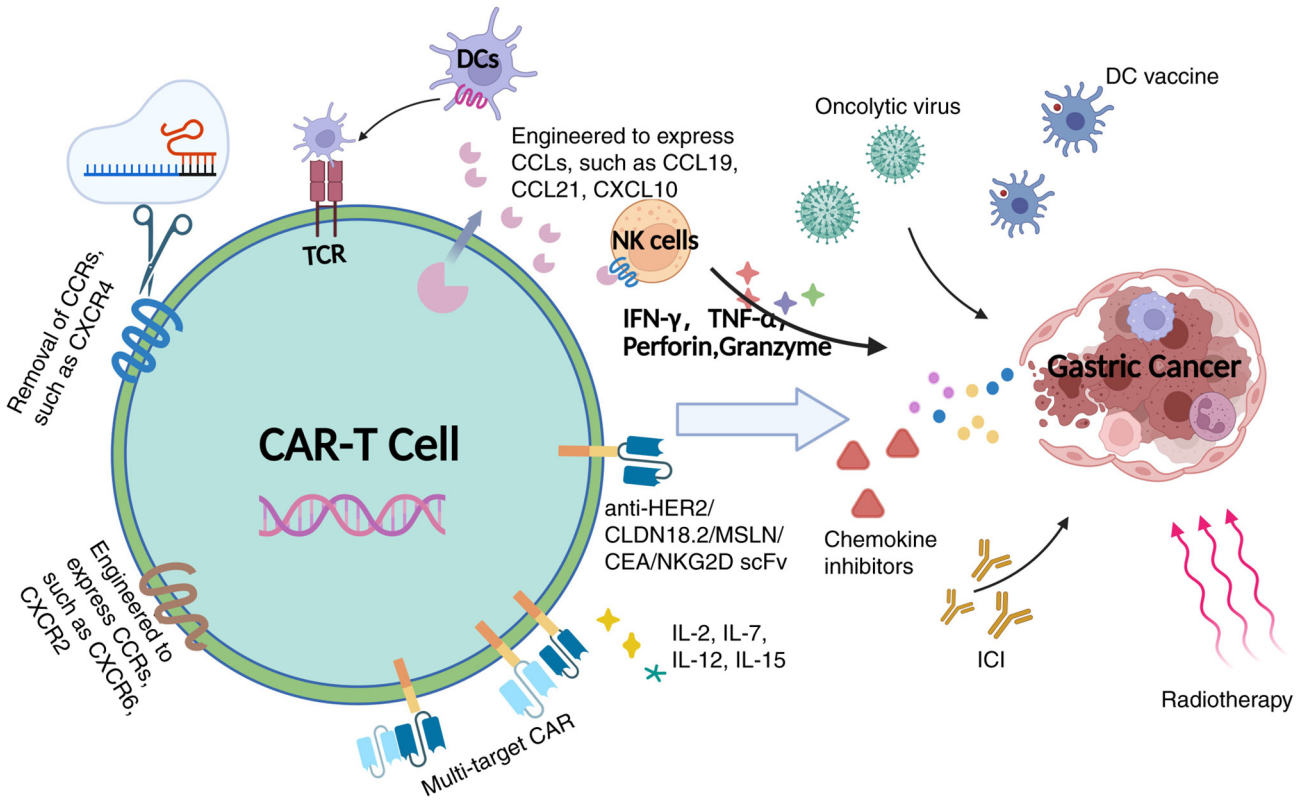

Figure 2. Chemokine-based strategy combined with next-generation CAR-T-cell therapy for solid tumors. CAR-T therapy has a number of obstacles in the treatment of solid tumors, such as immunosuppression and solid tumor barriers. Chemokine-based strategies can remodel the tumor immune microenvironment. CAR-T cells are engineered to express chemokine receptors (such as CXCR2 and CXCR6) or deplete immunosuppressive chemokine receptors (including CXCR4) to improve tumor infiltration. Arming with chemokines (CCL19, CCL21 and CXCL10) recruits DCs, natural killer cells and other antitumor immune cells, which secrete cytokines IL-2, IL-7, IL-12, IL-15, IFN-γ, perforin and granzyme to enhance antitumor immunity. Multi-target CAR structures reduce tumor escape and off-target cytotoxicity. In combination with ICIs, chemokine inhibitors, oncolytic viruses, DC vaccines and chemoradiotherapy promotes antitumor efficacy. CAR, chimeric antigen receptor; CLDN18.2, claudin 18.2; DC, dendritic cell; ICI, immune checkpoint inhibitor; IFN-γ, interferon-γ; MUC1, mucin 1; TCR, T-cell receptor.

hold notable potential for enhancing the efficacy of immunotherapy (Fig. 2).

Mechanistically, disruption of chemokine signaling can enhance T-cell trafficking. For example, CRISPR-Cas9-mediated knockout of chemokine receptors (such as CXCR4) on T cells (119) or use of CXCR4 inhibitors has been shown to release the T cells retained within lymphatic vessels, vascular endothelial cells or CAFs (105). Since certain tumor environments inhibit the expression of homing-related chemokine receptors, such as CXCR6, upregulating these receptors represents a promising therapeutic approach. Research has also demonstrated that engineering CAR-T cells to express chemokines such as CCL19, CCL21 and CXCL10 can increase the recruitment of DCs and NK cells, promoting antigen presentation and cytotoxic activity, and thereby enhancing antitumor immunity (74,120,121).

GC is characterized by marked heterogeneity. Distinct subtypes arise through different oncogenic mechanisms, resulting in substantial differences in TME features and chemokine expression profiles. According to The Cancer Genome Atlas classification, GC can be classified into four molecular subtypes: EBV-associated, microsatellite instability (MSI)-high, genomically stable (GS) and chromosomal instability (CIN). The EBV and MSI subtypes are usually linked to an immune-inflamed phenotype; these subtypes are characterized by increased T-cell infiltration and elevated expression of CXCL9/10/11 and CCL5, which are associated with improved responses to immunotherapy. By contrast, GS tumors exhibit an immunologically 'cold' phenotype, with enriched CAFs and MDSCs. Elevated levels of CXCL8, CXCL12 and CCL2 promote the recruitment of immunosuppressive cells and limit T-cell infiltration, suggesting that the CXCL8-CXCR2 axis may serve as a potential therapeutic target. CIN tumors display a fibroblast-rich and immunosuppressive microenvironment, in which CXCL8 and CXCL12 expression shows an upward trend and exacerbate immune suppression (122,123). Targeting pathways such as CXCR4 while performing CAR-T therapies, therefore, may represent an effective combinatorial strategy (124-126).

Despite these advances, the clinical safety of chemokine/chemokine receptor engineering combined with CAR-T therapy warrants careful evaluation. Notably, a marked expansion of $CXCR6^{+}$ cytotoxic T cells has been detected in the cerebrospinal fluid of patients with hematological malignancies, including diffuse large B-cell lymphoma, acute lymphoblastic leukemia, mantle cell lymphoma, follicular lymphoma, highly aggressive B-cell lymphoma and multiple myeloma, who developed immune effector cell-associated neurotoxicity syndrome (ICANS) following CAR-T therapy. Moreover, CXCL16 expression in myeloid cells has been

Table II. Combination of CAR-T-cell therapies with chemokine engineering strategies.

Chemokine/chemokine receptor	CAR-T-cell target antigens	Tumor	Chemokine axis	(Refs.)
CCL19	CD20/MSLN/ GPC3	Mastocytoma and pancreatic ductal adenocarcinoma/hepatocellular carcinoma	CCL19-CCR7	(74,76)
CCL19	NKG2D	Gastric cancer	CCL19-CCR7	(77)
CXCR1/CXCR2	CD70	Glioblastoma, ovarian and pancreatic cancer	CXCL8-CXCR1/ CXCR2	(90)
CXCL10	CLDN18.2	Gastric cancer	CXCL10-CXCR3	(99)
CXCR4	CD33	Acute myeloid leukemia	CXCL12-CXCR4	(26,108)
CCR2b	GD2	Neuroblastoma	CCL2-CCR2	(138)
CCR4	CD30	Hodgkin lymphoma	CCL17-CCR4	(139)
CCR6	EGFR	Lung cancer and gastric cancer	CCL20-CCR6	(140)
CCR8	MSLN	Pancreatic cancer	CCL1-CCR8	(141)
CXCR6	MSLN	Pancreatic cancer	CXCL16-CXCR6	(118)
CCL21	CLDN18.2	Pancreatic cancer, breast cancer and hepatocellular carcinoma	CCL21-CCR7	(142)

CAR, chimeric antigen receptor; CLDN18.2, claudin 18.2; GPC3, glypican-3; MSLN, mesothelin; NKG2D, natural killer group 2D.

shown to be positively associated with ICANS severity. These results suggest that the CXCL16-CXCR6 axis may contribute to neuroinflammation and the pathogenesis of ICANS (127). Furthermore, in a clinical trial where CCL19- and IL-7-armored CAR-T cells were applied, the overall safety was manageable but a subset of patients developed grade 3 cytokine release syndrome and neurotoxicity (128).

To mitigate these risks, current strategies include the incorporation of inducible safety switches, and the use of mRNA co-transfection to achieve transient expression of chemokines and their receptors (129,130). Careful optimization of chemokine-engineered CAR-T-cell strategies is essential to balance the efficacy and safety in treatment of GC.

Overall, combining CAR-T-cell therapy with chemokine engineering has the potential to effectively promote CAR-T-cell accumulation and enhance their cytotoxic response within tumors. CAR-T-cell therapies incorporating chemokine engineering strategies are currently under active investigation and have demonstrated promising efficacy (Table II). These tumor-targeting studies provide valuable insights for further development of CAR-T-cell therapy for GC. CAR-T cells designed against established GC targets, such as CLDN18.2, HER2, CEA, MSLN and NKG2D, in combination with chemokines, monoclonal antibodies, bispecific antibodies and ICIs, have shown promising therapeutic potential. For example, ICIs such as nivolumab, combined with anti-HER2 antibody (trastuzumab) and chemotherapy, have demonstrated clinical benefit in patients with HER2-positive GC (131,132). Dual-target CAR-T cells incorporating chemokine signaling, and the combination of immunotherapy and radiotherapy/chemotherapy have also been observed to overcome the limitations of 'immune-cold' tumors and to represent a key direction for future GC immunotherapy (133,134).

5. Conclusions

The TME in GC is a highly complex and dynamic ecosystem composed of diverse cellular components, including tumor cells, CAFs, immune cells and endothelial cells. These components interact extensively to regulate tumor progression, immune evasion and therapeutic responses. Additionally, these cellular components not only shape the structural and functional characteristics of the TME but also actively influence immune surveillance and resistance mechanisms.

Chemokines serve a central role in orchestrating cellular interactions within the TME by regulating immune cell trafficking, spatial distribution and functional polarization. For example, chemokines, such as CCL19, CCL21 and CXCL16, are involved in the recruitment and organization of immune cells, thereby affecting antitumor immune responses. Dysregulation of chemokine signaling contributes to the establishment of an immunosuppressive microenvironment by recruiting Tregs, MDSCs and TAMs; meanwhile, it simultaneously inhibits the infiltration and effector function of cytotoxic T lymphocytes. For example, chemokines CXCL8 and CXCL12 are commonly associated with immunosuppression and tumor progression, whereas chemokines CXCL9 and CXCL10 are context-dependent with either pro- or antitumor effects depending on the tumor type. Accordingly, targeting chemokine-receptor axes (such as CCR2, CCR4, CCR5, CXCR2, CXCR4) has emerged as a promising strategy to remodel the TME, enhance antitumor immunity and improve therapeutic efficacy in cancers.

Despite substantial advances, the efficacy of CAR-T therapy in solid tumors such as GC remains constrained by poor tumor infiltration, antigen heterogeneity and an immunosuppressive microenvironment. Integrating chemokine-based

strategies into CAR-T design, such as engineering chemokine receptors, secreting chemokines or combining with chemokine inhibitors, provides a rational approach to overcome these barriers. These strategies can enhance T-cell trafficking, promote immune cell recruitment, convert 'cold' tumors into 'hot' tumors and foster immunologically active environments.

Chemokine-based combination strategies, including dual-target CAR-T-cell therapies, mRNA co-transfection approaches, ICIs, DC vaccine, oncolytic virus-based immunology and conventional therapies (such as radiotherapy and chemotherapy), hold great promise for improving therapeutic outcomes in patients with GC. However, a number of challenges remain, particularly regarding safety, off-target effects and the lack of physiologically relevant humanized models for pre-clinical evaluation. Future efforts should focus on optimizing engineering strategies, refining combination regimens and developing advanced model systems to better predict clinical efficacy.

Overall, an improved understanding of the interplay between cellular components and chemokine networks within the TME in GC is essential for developing more effective and personalized immunotherapeutic strategies. This may contribute to improving clinical outcomes for patients with GC.

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ZL conceptualized, designed, wrote, edited and reviewed the manuscript. ZX provided supervision and revised the manuscript. Both authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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