frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 16 July 2024
DOI 10.3389/fimmu.2024.1443366

OPEN ACCESS

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RECEIVED 03 June 2024
ACCEPTED 01 July 2024
PUBLISHED 16 July 2024

CITATION
Jung H and Paust S (2024) Chemokines in the tumor microenvironment: implications for lung cancer and immunotherapy.
Front. Immunol. 15:1443366.
doi: 10.3389/fimmu.2024.1443366

Chemokines in the tumor microenvironment: implications for lung cancer and immunotherapy

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The tumor microenvironment (TME) is a complex interconnected network of immune cells, fibroblasts, blood vessels, and extracellular matrix surrounding the tumor. Because of its immunosuppressive nature, the TME can pose a challenge for cancer immunotherapies targeting solid tumors. Chemokines have emerged as a crucial element in enhancing the efficacy of cancer immunotherapy, playing a direct role in immune cell signaling within the TME and facilitating immune cell migration towards cancer cells. However, chemokine ligands and their receptors exhibit context-dependent diversity, necessitating evaluation of their tumor-promoting or inhibitory effects based on tumor type and immune cell characteristics. This review explores the role of chemokines in tumor immunity and metastasis in the context of the TME. We also discuss current chemokine-related advances in cancer immunotherapy research, with a particular focus on lung cancer, a common cancer with a low survival rate and limited immunotherapy options.

KEYWORDS

chemokines, immune cells, cancer, tumor microenvironment, immunotherapy, lung cancer

Abbreviations: AKT, Ak strain transforming; APCs, Antigen-presenting cells; CAR, Chimeric antigen receptor; CCL, C-C motif chemokine ligand; CCR, C-C motif chemokine receptor; cDC1s, Type I conventional DCs; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; DCs, Dendritic cells; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitor; EMT, Epithelial-mesenchymal transition; ERK, Extracellular signal-regulated kinase; ICIs, Immune checkpoint inhibitors; IL, Interleukin; IFNγ, Interferon gamma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; MAPK, Mitogen-activated protein kinase; MDSCs, Myeloid-derived suppressor cells; MHC, Major histocompatibility class; MPEs, Malignant pleural effusions; Nir1, N-terminal domain interacting receptor; NK, Natural killer; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; PD-L1, Programmed death-ligand 1; PI3K, Phosphatidylinositol 3-kinase; SCLC, Small cell lung cancer; SDF1, stromal cell-derived factor 1; TADCs, Tumor associated-dendritic cells; TAMs, Tumor-associated macrophages; TNM, Tumor node metastasis; TILs, Tumor-infiltrating lymphocytes; TME, Tumor microenvironment; Treg, Regulatory T.

1 Introduction

Chemokines, also known as chemotactic cytokines, are small secreted proteins that play a crucial role in controlling the migration of immune cells to specific tissues (1). Chemokines interact with seven transmembrane G protein-coupled receptors, initiating intracellular signaling that governs cell polarization, adhesion, and movement. Structurally, chemokines are categorized into four families: CXC, CC, CX3C, and C, which are named for the number and location of cysteine residues (C) on the amino terminus of the protein. Cell type-specific epigenetically regulated chemokine receptor expression by distinct leukocyte populations ensures that chemokine gradients can regulate the influx of immune effector cells to sites of inflammation, or, during homeostasis, immune cells to their respective resident tissues (2). Cancer is one of the situations wherein chemokines exert their influence, taking place primarily within the tumor microenvironment (TME).

Cancer immunotherapy has emerged as a significant treatment modality, sparking heightened interest in cancer immunity research. Within the field, there has been an increased interest in the use of immune-related signaling proteins like cytokines and chemokines, as well as diverse immune checkpoint molecules, and the identification of neoantigens (3). These elements have been evaluated as pivotal targets for therapeutic interventions and can also utilized as biomarkers in cancer immunotherapy evaluations. While adoptive cell therapy has demonstrated remarkable success in treating hematologic cancers, for most solid tumors, including lung, pancreatic, breast, and liver cancers, effective cancer immunotherapies have yet to be developed, or if a therapy is available, tumors have proven resistant to treatment (4). This resistance is largely attributed to the intricate and dynamic nature of the tumor microenvironment specific to solid tumors, which presents a significant barrier to effective immune attack (5).

Lung cancer is the second most common cancer and the leading cause of cancer-related deaths worldwide (6). Lung tumors are broadly classified into two categories: non-small cell lung cancer (NSCLC), which account for approximately 80–85% of all lung cancer cases, and small cell lung cancer (SCLC), which represent the remaining 15% of occurrences. NSCLC can be further categorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (3). Unfortunately, the survival rates for metastatic lung cancer, including both NSCLC and SCLC, are generally poor, with a five-year survival rate of only around 4% (7).

Recent technological advancements have enhanced our comprehension of the intricate molecular mechanisms underlying the immunogenicity of lung cancer. Consequently, various immunotherapies, such as therapeutic vaccines, immunomodulators, and monoclonal antibodies targeting checkpoint inhibitors have emerged for lung cancer management. Nonetheless, each approach comes with unique benefits and caveats, prompting the exploration of combined therapies and immunotherapy enhancers (7). Further investigation is needed to identify the optimal combination of immunotherapies, with the potential inclusion of chemokines in this endeavor.

This review will explore the role of chemokines in modulating immune cells within the TME. We will describe how chemokines regulate various immune cell types and facilitate interactions that impact tumor growth and metastasis. Additionally, we will discuss potential strategies for leveraging chemokines in cancer therapy. Finally, we will examine lung cancer-specific chemokine research, including basic and pre-clinical studies, as well as ongoing clinical applications that focus on TME immunity.

2 Chemokines in the TME

The TME is a complex interconnected network of immune cells, fibroblasts, blood vessels, and extracellular matrix surrounding the tumor and involved in tumor growth and metastasis (8, 9). The genetic, immunologic, and metabolomic diversity of the TME can result in varied treatment outcomes within cancer and be a major cause of therapy resistance (10, 11). Chemokines are involved in regulating immune cell infiltration and shaping tumor progression. Since chemokines are pleiotropic, their combinatorial intratumoral expression can have complex and diverse tumor-promoting or tumor-fighting effects (Figure 1). Therefore, depending on the type of tumor and its immune infiltration, it is necessary to individually assess whether chemokine signaling promotes or inhibits tumor growth.

2.1 Impact of chemokines on tumor immunity

Immune cells such as natural killer (NK) cells, dendritic cells (DCs), macrophages, and T cells are crucial tumor-fighting components of the TME (12). However, cancer cells also secrete chemokines, altering the TME and its immune cell composition to be more tumor-promoting (13) (Figure 2A). The underlying mechanisms by which these immune cell populations and cancer cell-secreted chemokines interact are complex, and understanding them is crucial for cancer research progress (14, 15). In this section, we will discuss how individual chemokines modulate the innate and adaptive immune response in healthy and malignant tissues, before discussing strategies to use chemokines in cancer therapy in section 3, and effects of chemokines on lung cancer immunity in section 4.

2.1.1 NK cells

NK cells are a type of cytotoxic lymphocyte of the innate immune system. NK cells are inhibited by the robust expression of major histocompatibility complex class (MHC) I molecules, which mark potential target cells as 'self' and trigger inhibitory killer cell immunoglobulin-like receptor signaling to prevent NK cell activation. Cells with low MHC-I expression are considered as 'missing self' and are preferred targets for NK cell-mediated cytotoxicity and other effector functions (16), provided NK activating signals (*e.g.*, in the form of stress ligands) are also present. However, malignant cells often upregulate stress ligands

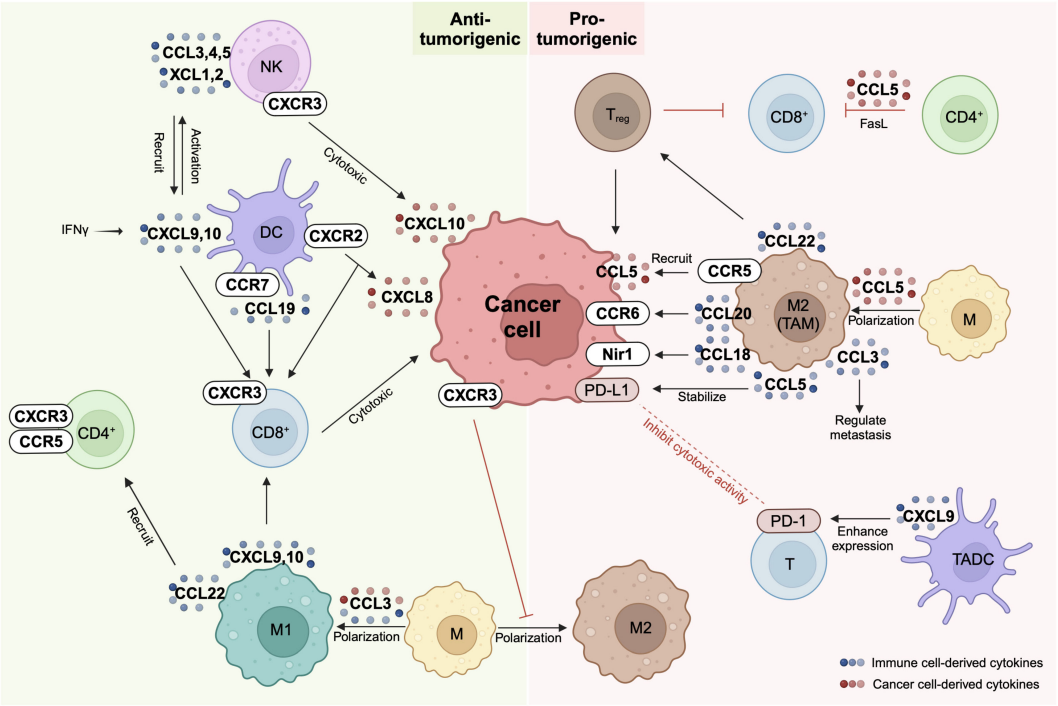

FIGURE 1
Chemokine network between immune cells and cancer cells. Chemokine receptors (CCR or CXCR) and their ligands (CCL or CXCL) are expressed on cancer cells and a variety of immune cells including natural killer (NK) cells, dendritic cells (DC), macrophages (M), and T cells. The same chemokine can exhibit either anti-tumorigenic or pro-tumorigenic properties depending on the specific cell type it interacts with. For instance, macrophages display anti-tumorigenic characteristics when polarized to M1 and pro-tumorigenic attributes when polarized to M2. NK cells and CD8+ T cells contribute to cancer cell elimination through cytotoxic actions, representing pivotal players in the immune response against tumors. On the other hand, PD-1/PD-L1 interactions occurring between cancer cells and T cells serve to suppress T cell activity, contributing to immune evasion. Additionally, regulatory T (Treg) cells, tumor-associated dendritic cells (TADC), and M2 macrophages collectively contribute to the establishment of an immunosuppressive environment within the tumor microenvironment. These intricacies highlight the complex interplay between various immune cell types and the tumor cells in shaping the dynamics of cancer progression and response to immunotherapy. Created with BioRender.com.

and down-regulate MHC-I to escape cytotoxic T-cell immunity, thereby becoming 'missing self' targets. Thereby, NK cells play an important role in early cancer defense. Chemokine signaling can augment anti-tumor immunity, as C-X-C motif chemokine receptor (CXCR) 3 expressed on NK cells senses C-X-C motif chemokine ligand (CXCL) 10 secreted by cancer cells and exerts cytotoxic activity at the cancer site (17). In addition to their direct anti-tumor functions, NK cells secrete chemokines to recruit key

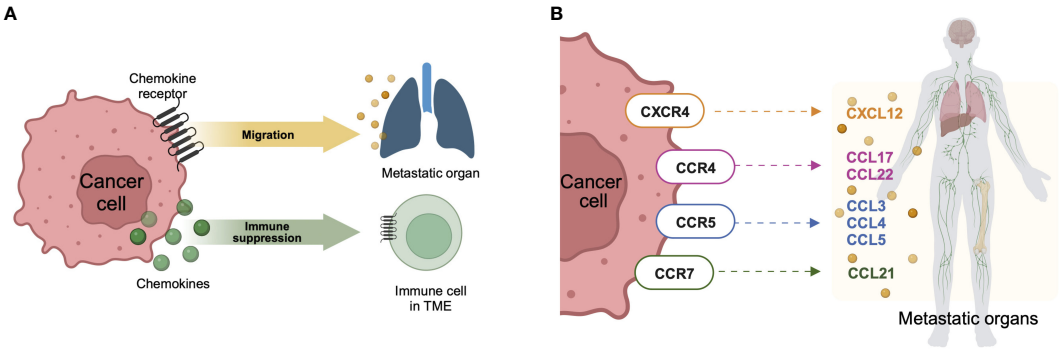

FIGURE 2
Chemokine network in metastasis. **(A)** When cancer cells express chemokine receptors, their role extends to facilitating migration towards chemokine ligands expressed in metastatic organs. In this context, these receptors play a crucial role in directing the movement of cancer cells within the body. Conversely, when cancer cells express chemokine ligands, their impact is primarily on the immune cells within the tumor microenvironment, contributing to the establishment of immunosuppression. This dual interaction underscores the intricate balance between cancer cells and the surrounding microenvironment, influencing both the metastatic potential of the cancer and the immune response within the tumor. **(B)** Chemokine receptor-ligand axes are involved in metastasis. These specific axes of chemokine receptors expressed on cancer cells and chemokine ligands expressed in metastatic organs are commonly involved in the migration of cancer cells, leading to metastasis. Created with BioRender.com.

immune cell populations required for robust anti-tumor immunity. Indeed, intra-tumoral cytotoxic NK cells express high levels of C-C motif chemokine ligand (CCL) 3, CCL4, CCL4L2, and CCL5 transcripts, while additional NK cell subsets express X-C motif chemokine ligand (XCL) 1 and XCL2 transcripts (18). When secreted by intratumoral NK cells, XCL1, XCL2, and CCL5 serve as chemoattractants for type 1 conventional DCs (cDC1s), augmenting the recruitment of cDC1s into the TME where these powerful antigen-presenting cells can activate the cytotoxic $CD8^+$ T lymphocytes (CTLs) for tumor attack (19, 20). In addition to aiding cDC-CTL interactions, Interleukin (IL)-18-primed "helper" NK cells secrete CCL3 and CCL4 to attract immature DCs to stimulate intratumoral $CD8^+$ T cells via CCL5, CXCL9, and CXCL10 (21).

2.1.2 DCs

DCs are professional antigen-presenting cells (APCs) bridging innate and adaptive immunity by initiating immune tolerance and antigen-specific immunity (22). In tumors, DCs present tumor antigens to elicit an antigen-specific T-cell response (23). The CXCL9/CXCL10-CXCR3 axis is crucial for NK cell-DC-$CD8^+$ T cell crosstalk and anti-tumor immune response (24). $CD103^+$ DCs recruit NK cells by releasing CXCL9, inducing the upregulation of the NK cells-activating receptor NKG2D while downregulating the inhibitory NK cell-expressed receptor NKG2A (25). The expression of CXCL9 in DCs is induced by interferon-gamma (IFN-γ) (26) and can be further upregulated with immune checkpoint therapies targeting TIM-3 (27) or CD47 (25). However, when secreted by tumor associated-dendritic cells (TADCs), CXCL9 can also enhance the expression of the checkpoint molecule ligand programmed death-ligand 1 (PD-L1), thereby attenuating anti-tumor T cell immunity via the PD-1/PD-L1 pathway (28). The CCL19/C-C motif chemokine receptor (CCR) 7 axis poses an anti-cancer property that both $CCL19^+$ DCs (29) and $CCR7^+$ DCs (30) augment $CD8^+$ T cell immunity. Lastly, CXCR2 expression by DCs induces their migration into the tumor through the CXCL8-CXCR2 axis (31, 32), since CXCL8, a CXCR2 ligand, is expressed by endothelial cells, tumor-associated macrophages (TAMs), and cancer cells. This CXCL8-CXCR2-mediated recruitment of DCs towards the tumor site induces DC activation and $CD8^+$ T cell infiltration.

2.1.3 T cells

T cells are an essential component of adaptive immunity. Once primed and activated by APCs, T cells migrate to the tumor site and exert antitumor activity in a process called chemotaxis, which, as its name implies, is triggered by chemokines (33). CCL5 and the IFNγ-inducible chemokines CXCL9/10/11 are critical components of this process. Tumor-derived CCL5 and APC-derived CXCL9 enhance $CD8^+$ T cell infiltration in solid tumors; this effect is more notable for CXCL9 (26, 34, 35). $CD4^+$ Th1-polarized effector memory cells expressing CXCR3 and CCR5, the receptors for CXCL9/10/11 and CCL5, respectively, are another significant component of tumor-infiltrating lymphocytes (TILs). Indeed, the proportion of intratumoral $CCR5^+CXCR3^+CD4^+$ cells has been observed to be inversely proportional to metastasis formation in renal carcinoma patients (36). In addition, CD40-signaling-induced CCL5 elicits tumor infiltration by $CD4^+$ T cells and enables immunosuppression of cancer growth (37). In pancreatic ductal adenocarcinoma, CCL4, CCL5, CXCL9, and CXCL10 are directly associated with $CD8^+$ T-cell infiltration (38). However, CCL5 can also suppress T cell immunity at the tumor site and may even promote tumor immune evasion (39) by inducing tumor infiltration by regulatory T (Treg) cells, impairing the cytotoxic activity of $CD8^+$ T cells (40). In addition, cancer cells can stimulate $CD4^+$ T cells to secrete CCL5, inducing Fas-mediated apoptosis of $CD8^+$ T cells (41, 42).

2.1.4 Macrophages

Alongside DCs, macrophages are major APCs and are an important component of innate immunity. Macrophages are plastic cells that can be polarized into two phenotypes: pro-inflammatory M1 macrophages and anti-inflammatory/immunosuppressive M2 macrophages. Tumor-associated macrophages (TAMs) are similar to M2 macrophages, except that TAMs express Fc receptors for IgG, C-type lectin, and heat shock proteins and secrete CCL2 and CCL5 (43). TAMs-secreted CCL5 stabilizes tumor-expressed PD-L1, inhibiting the cytotoxic activity of T cells and inducing immune escape (44). On the other hand, cancer cell-secreted CCL5 induces the polarization of monocytes into M2 macrophages and recruits $CCR5^+$ TAMs (45–47). Another chemokine axis regulating TAM activity is CCR6-stimulation by CCL20. Circular RNAs secreted by cancer cells stimulate TAMs to secrete CCL20 (48), increasing TAM migration and the invasion of CCR6-expressing tumors while also inducing epithelial-mesenchymal transition (EMT) (49, 50). The CXCL9/CXCL10-CXCR3 is another axis with anti-tumor properties. Following dual PD-1/CTLA-4 blockade, macrophages secrete CXCL9 and CXCL10, increasing tumor infiltration of $CD8^+$ T cells (51). Furthermore, the expression of CXCR3 on cancer cells reduces polarization into TAMs; a study of gastric cancer patients demonstrated that those who expressed more CXCR3 had a better prognosis (52). Lastly, previous studies of CCL3 (a CCR5 ligand) and CCL22 (a CCR4 ligand) have shown conflicting results. While TAMs induce cancer cell migration and regulate metastasis by secreting CCL3 (53), docetaxel, a classical anti-mitotic chemotherapy drug, triggers the secretion of CCL3 from macrophages and cancer cells and induces polarization towards M1 macrophages, subsequently facilitating cancer cell phagocytosis (54). Similarly, macrophage-derived CCL22 can either suppress tumor immunity by increasing Treg cell tumor infiltration (55) or promote tumor immunity by recruiting helper T cells (56).

2.2 Metastasis regulation by chemokines and chemokine receptors

Some chemokines and their receptors aid in TME formation by promoting tumor cell proliferation and metastasis. Since metastatic cancer has a low chance of remission, and most cancer-related deaths result from metastatic cancer rather than primary cancer

(57), chemokines responsible for metastasis can be potential therapeutic targets or prognostic markers (58, 59). Although most chemokine receptors can be expressed on both immune and cancer cells, in this review, we focus on cancer cell-expressed chemokine receptors because of their ability to increase a tumor's metastatic potential by inducing EMT when chemokine receptor-expressing cancer cells migrate to metastatic sites rich in chemokine ligands (Figure 2B).

CXCR4 is the receptor for CXCL12, also called stromal cell-derived factor 1 (SDF1), and is the most widely expressed chemokine receptor in human cancer (60). CXCR4 is highly expressed by human cancer cells and is involved in metastasis formation, as confirmed experimentally by the *in vivo*-neutralization of CXCR4 (61). Studies in solid tumors, as such the depletion of the transcription factor forkhead box P3 in mammary epithelial cells (62), the overexpression of transcription factor 12 in hepatocellular carcinoma (63), and the acetylation of transcription factor Krüppel-like factor 5 in prostate cancer (64) have been performed to evaluate the effects of CXCR4 modulation on tumor growth. Additionally, microRNA-sequencing from SCLC patient serum revealed that miR-1 expression reduces tumor growth and metastasis by targeting the CXCR4/FOXM1/RRM2 axis (65). Upregulation of CXCR4 increases chemotaxis of tumor cells towards pro-metastatic CXCL12 promoting metastasis in solid tumors, as well as tumor angiogenesis and tumor growth through the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase/Ak strain transforming (PI3K/AKT) signaling pathways (63, 66–68). The CXCL12-CXCR4 axis is also related to cisplatin-induced metastasis which is known to be the long-term detrimental effect of platinum-based chemotherapy (69). Cisplatin activates the CXCL12-CXCR4 axis and induces lung metastasis by regulating the expansion of inflammatory monocytes in mouse model of lung cancer metastasis (69). Platinum-treated clinical samples of NSCLC show elevated CXCL12 levels, which were associated with worse clinical outcomes (69).High levels of CXCL12, the ligand for CXCR4, have been found in metastasis in organs such as the lung, liver, bone marrow, and lymph nodes through the recruitment of CXCR4-expressing cancer cells (63, 70–72).

CCR4 and its ligands CCL17 and CCL22 are also involved in cancer cell migration. The expression of CCL17 and CCL22 is increased in the lung, liver, and brain of tumor-bearing nude mice with an increased malignancy phenotype of cancer cells (73). CCR4 was highly expressed by melanoma cells in brain metastatic regions with altered AKT phosphorylation patterns (74, 75). Moreover, CCR4 facilitated metastasis through the ERK signaling pathway in colorectal cancer (76), bladder cancer (77), hepatocellular carcinoma (78), and lung cancer (79). As such, CCR4 targeting could enable novel cancer immunotherapies for solid tumors.

The chemokine receptor CCR5 binds with affinity to CCL3, CCL4, CCL5, and CCL8. Among CCR5 ligands, its interaction with CCL5 has been studied the most. These studies established the CCR5-CCL5 axis's ability to drive cancer progression and recruit tumor-infiltrating leukocytes in several cancer types (80). CCR5 is overexpressed in lymphoma (81, 82), hepatocellular carcinoma (83), pancreatic cancer (80), colorectal cancer (84), and many other cancers (85–87). In addition, high tissue or plasma levels of CCL5 correlate with unfavorable outcomes in pancreatic cancer patients (80). Through PI3K/AKT signaling pathways, the CCL5-CCR5 axis induces cancer cell survival, invasion, migration, and metastasis (83, 85, 87). As part of the CCR5 metastatic process, the CCL3-CCR5 (88, 89) and the CCL4-CCR5 (90, 91) axes also drive cancer cell invasion and migration.

Another receptor involved in metastasis is CCR7. CCR7 is crucial for immune cell homing of immune cells to lymphoid organs and is normally expressed on mature DCs and naïve lymphocytes (92). Due to their lymphoid origins, many leukemias and lymphomas also express CCR7 (93), enabling lymph node metastasis (94, 95). Of the two ligands of CCR7, CCL19, and CCL21, only CCL21 is associated with metastasis, contributing to lymphatic metastasis in pancreatic (94), lung (95–97), breast (61, 98), and other cancers (99–102) via ERK signaling. Moreover, CCR7 enhances angiogenesis by increasing vascular endothelial growth factor (96, 102, 103). Tumor necrosis factor -α, a proinflammatory cytokine, can increase CCR7 expression in cancer cells (104), promoting the production of CCL21 in human lymphatic endothelial cells (97).

Other chemokine axes, such as the CXCL8-CXCR1/2 axis (105, 106), the CXCL9-CXCR3 axis (107, 108), the CXCL13-CXCR5 axis (109), the CCL2-CCR2 axis (110, 111), and the CCL20-CCR6 axis (112, 113), are also involved in cancer metastasis; the chemokine axis can vary depending on the type of cancer (114–116). The wide variety of chemokine receptors involved in metastasis underscores the importance of assessing changes in chemokine expression as part of cancer treatments to predict cancer and metastasis progression and to inform treatment options.

3 Strategies to use chemokines in cancer therapy

Chemokines have been validated as disease targets through genetic depletion and antibody neutralization. Chemokine receptors are also among the most structurally well-studied class A family of G protein-coupled receptors, leading to their use in many drug discovery programs (117). However, using a chemokine itself as a drug presents particular challenges. One major difficulty lies in the complexity and high redundancy of the chemokine system. Chemokines can bind to multiple receptors and act as an agonist for one receptor while acting as an antagonist for another. Similarly, a chemokine receptor can have an affinity for various chemokines exhibiting biased signaling. Moreover, a cell can express several chemokine receptors, varying their expression by disease state (118). In addition, chemokine receptors can form homo- and hetero-dimers, making it difficult to develop drugs that precisely target isolated chemokine/chemokine receptor pathways (119). These considerations make the pharmaceutical targeting of chemokine receptors challenging (117). Indeed, adverse effects from the use of chemokine antagonists have been reported: the clinical trial of aplaviroc, a CCR5 antagonist, was terminated prematurely due to compound-induced liver toxicity (120).

Nevertheless, using chemokines in cancer therapy can be valuable in guiding immune cells and cancer cells to specific locations, influencing whether the TME promotes or suppresses tumor growth. Efforts are ongoing to address the challenges associated with the development of chemokine drugs and therapies. These may include combining chemokines with other existing therapies, modification of chemokine expression by immune cells, or utilizing chemokines for tumor targeting.

3.1 Adoptive cell therapies

Adoptive cell therapies, such as chimeric antigen receptor (CAR)-T cell therapy and NK cell-based immunotherapy, have proven to be revolutionary treatments for certain subsets of B cell leukemia and lymphoma (121). Over the past decade, adoptive cell therapies have been investigated for the treatment of solid tumors. However, the anti-cancer activity of infused immune cells can be limited at least in part by a lack of penetrance into the solid tumor and the tumor's immunosuppressive environment (4), and in the case of CAR-T cell-therapy, limited tumor neoantigen availability, and insufficient CAR-T cell infiltration of the tumor and metastatic tissues (5). To overcome these limitations, strategic expression of chemokine receptors can be used to augment solid tumor immunotherapy. An example of this is the forced expression of the CCL2 receptor CCR2b in B7-H3-specific CAR-T cells, which significantly enhanced the anti-tumor activity to brain metastases in mouse xenograft models by enabling CAR-T cells to effectively cross the blood-brain barrier (122). Similarly, the expression of IL-7 and CCL19 improved the anti-tumor potential of CAR-T cells by augmenting their activation and boosting the generation of memory responses for both recipient conventional T cells and administered CAR-T cells against mastocytoma in mice (123).

NK cells are also being developed as immunotherapy infusion products (124) as an alternative to CAR-T cell therapies with significant toxicity issues (121). CCR7-expressing CAR NK cells were shown to be more effective than control CAR-NK cells in controlling tumors via the CCL19-CCR7 axis both *in vitro* and in a murine lymphoma xenograft model (125). Further, CXCR4 expressing CAR-NK cells exhibited an enhanced ability to migrate towards a CCL12 gradient while maintaining functional cytolytic activity towards target cancer cells ($CD19^+$ Nalm-6 cells) *in vitro* (126). In addition to directly expressing chemokines in CAR-engineered cells, chemokines can also be used to indirectly enhance the effectiveness of CAR cell therapy. For example, CXCL11-armed oncolytic adenoviruses were used as an adjuvant in CAR-T cell therapy, reprogramming the immunosuppressive TME in a syngeneic glioblastoma mice model (127).

Another approach is to regulate the endogenous gene expression in immune cells to modulate the expression of chemokines, followed by adoptive cell therapy. To exploit the CCL5-CCR5 axis that allows NK cell infiltration of tumors, researchers have used oncolytic vaccinia virus Western Reserve strain to increase CCR5 expression on NK cells and CCL5 expression on cancer cells (128). Comparisons of NK cells from tissues of patients with various cancers and healthy individuals showed that NK cells from cancer patients had lower expression of CCR5. When NK cells were genetically engineered to overexpress CCR5 and then infused, survival rates increased in mice. Simultaneously increasing CCL5 expression on cancer cells increased the anti-cancer effect even more (128). In a different study, NK cells were engineered to overexpress CCR2B and CCR4 to induce migration toward CCL2- and CCL22-expressing tumor cells, respectively (129). Also noteworthy is that in both studies, NK cells were genetically engineered without their functional impairment.

3.2 Combination of chemokines with immune checkpoint inhibitors (ICIs)

ICIs are powerful treatments that have expanded the field of cancer immunotherapy to allow the treatment of solid malignancies. Currently, FDA-approved ICIs include pembrolizumab, nivolumab, cemiplimab, dostarlimab, toripalimab, retifanlimab (PD-1-specific antibodies), ipilimumab, tremelimumab (CTLA-4-specific antibody), atezolizumab, avelumab, and durvalumab (PD-L1-specific antibodies) (130). However, treatment efficacy still varies between patients. For example, in solid tumors, such as NSCLC, ICIs can be used when other therapies have failed, with conflicting long-term results. While some studies have shown no benefit to long-term ICI treatments (131, 132), others have reported positive outcomes with pembrolizumab two (133) and five years post-treatment (134). Because the TME can play a role in modulating ICI efficacy, chemokines can be used to overcome TME-induced immunosuppression and increase the response rate to ICI (135). One example of this is a study of 27 NSCLC patients, in which a positive correlation was identified between the patients' CXCL13 expression and observed ICI efficacy. In a subsequent animal model-based mechanistic study administering recombinant CXCL13 to mice with lung cancer, it was demonstrated that CXCL13 treatment enhanced therapeutic PD-1 blockade by increasing antigen-experienced T cell subsets (135). Another example of this is a phase IIa clinical trial (NCT02826486) of a combination of the CXCR4 antagonist BL-8040 and pembrolizumab in patients with metastatic pancreatic duct adenocarcinoma (PDAC), where BL-8040 increased $CD8^+$ effector T cell tumor infiltration, decreased myeloid-derived suppressor cells (MDSCs), and further decreased circulating Treg cells, resulting in a favorable outcome (136).

3.3 Use of nanoparticles for chemokine delivery

Researchers have developed nanoparticles to enhance the delivery of chemokines in cancer therapy while performing multiple functions. For example, using NPs to deliver maraviroc, a small molecule inhibitor of CCR5, improved bone marrow residence time while reducing leukemic burden compared to treatment with maraviroc alone in mouse models (137). NPs have been developed using different approaches to enable the use of CXCR4 in cancer therapy. For example, the AMD-NP-PTX nanocomplex was developed for

targeting ovarian cancer (136). It contains a small molecule antagonist for CXCR4 (AMD3100) and paclitaxel (PTX), a common chemotherapy drug. Due to the overexpression of CXCR4 in ovarian cancer, AMD-NP-PTX can be effectively delivered to the cancer site, inhibiting the CXCL12-CXCR4 axis and exerting chemotherapeutic activity with reduced off-target toxicity. Similarly, AMD31100 coated on synthetic protein nanoparticles (AMD3100-SPNPs) delivered to a glioblastoma mouse model inhibited tumor proliferation and reduced infiltration of $CXCR4^+$ MDSCs while overcoming poor pharmacokinetic properties of AMD3100 and restoring the blood-brain barrier (138). CXCR4 antagonistic nanoparticles have also been designed to enhance the response rate of anti–PD-L1 therapy to treat lung cancer (139). These nanoparticles increased the effector T cell infiltration in solid tumors by reducing the tumor's fibrosis and tumor-resident MDSCs and Treg cells, subsequently enhancing the effectiveness of the PD-1/PD-L1 immunotherapy both *in vivo* and *in vitro*. Alternatively, NPs can be used to upregulate chemokine-related genes in cells rather than to directly deliver chemokine-related drugs to the tumor. Polymeric NPs containing CXCR4 DNA were used to upregulate CXCR4 in human adipose-derived stem cells to target tumor hypoxia (140). In another study, a hydrogel nanoparticle complex, LPR@CHG, containing lipid-immune regulatory factor 5 mRNA/CCL5 siRNA (LPR) nanoparticle complexes coated with chitosan/HTCC/glycerophosphate was designed as a potential pancreatic cancer treatment (141). This hydrogel complex downregulated CCL5 secretion of tumor cells, which contributed to an increase in M1 macrophages and elicited a T cell-mediated immune response, ultimately controlling pancreatic cancer in mice.

4 The effects of chemokines on lung cancer immunity

Lung tissue represents a unique microenvironment supportive of primary lung carcinoma development and metastases originating from tumors outside the lung (142). Recent advances in understanding the tumor-reprogrammed microenvironment have led to the development of targeted therapies for lung cancer. Targeting angiogenesis and immune cells has shown promise, sparking interest in understanding other TME components to improve clinical outcomes in lung cancer (142). In this context, chemokines affect tumor growth, metastasis, and even the effectiveness of radiation therapy by involving various cellular interactions and altering TME (143). In this section, we will discuss chemokine networks in lung TME (Figure 3), highlighting recent chemokine-related advances in lung cancer immunotherapy.

4.1 Preclinical studies of chemokines in lung cancer

In a study of NSCLC patients with metastatic disease, a high expression of CXCR1 was associated with a poor prognosis reflected by the patient's tumor node metastasis (TNM) stage (144). The expression of CXCR1 was positively correlated with tumoral neutrophils and macrophages and with the polarization of macrophages to the immunosuppressive M2 phenotype. Furthermore, patients resistant to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) treatment expressed high levels of CXCR1. In these patients, CXCR1 modulated the tumor microenvironment as well as the PI3K/AKT and ERK pathways, which are shared by CXCR1 and EGFR-TKI. These findings suggest that CXCR1 could be a therapeutic target for NSCLC.

CXCR2 is mainly expressed by neutrophils and associated with pro-tumorigenic properties, especially angiogenesis. Among the ligands of CXCR2, CXCL1, 5, 7, and 8 are considered major angiogenic chemokines in NSCLC (145), with the overall level of angiogenic chemokines being the strongest predictor of tumor vessel density in NSCLC (146). Additionally, lung tumors in $CXCR2^{-/-}$ mice presented increased necrosis and reduced vascularity (147). Indeed, tumor-infiltrating $CXCR2^+$ neutrophils play a significant role in shielding tumor cells from $CD8^+$ T and NK cell-mediated cytotoxicity. Their presence contributes to the recruitment of Treg cells and facilitates tumor cell metastasis. In a murine lung cancer model, $CXCR2^+$ neutrophils TGF-β and Arg-1 were significantly increased, causing immunosuppression and allowing tumor cells to escape immune attack. In contrast, CXCR2 inhibition reduced neutrophil infiltration and promoted $CD8^+$ T cell activation (148). Single-cell RNA analysis of human lung squamous cell carcinoma (LUSC) tissues also showed an increase in these tumor-infiltrating neutrophils, characterized by CXCL8-CXCR2 expression (149). In addition, CXCR2 regulated Treg cell migration into malignant pleural effusions (MPEs) via the miR141-CXCL1-CXCR2 pathway, decreasing the median survival of NSCLC patients with MPE (150).

Despite the important role of the CXCL9/CXCL10-CXCR3 axis in NK/DC/$CD8^+$ T cell crosstalk, this pathway has been insufficiently studied in the context of lung cancer. What we do know is that the commensal microbiota may influence the development of lung cancer in a *Kras*-driven mouse model, where an antibiotic-treated group exhibited high expression of CXCL9 and CXCR3, resulting in increased recruitment of NK cells and $CD8^+$ T cells to the tumor, highlighting the importance of the CXCL9-CXCR3 axis in lung cancer immunity (151). However, a different study revealed that CXCL10-CXCR3 induced resistance to EGFR-TKI treatment in a transgenic lung cancer mouse model (152). During early EGFR-TKI treatment, increased CXCL10 levels stimulated oncogenic signaling in persisting tumor cells, contributing to EGFR-TKI resistance through autocrine and paracrine pathways. These contrasting results highlight the need for additional work to address the contributions of the CXCL9/CXCL10-CXCR3 to lung cancer immunity.

High CXCR4 expression in NSCLC including lung adenocarcinoma (LUAD) and LUSC is correlated to poor patient prognosis (153, 154). Paradoxically, the $CXCR4^{high}$ NSCLC tissues recruit more immune cells into NSCLC tissues with increased immune checkpoint expression and bring a higher response rate to immunotherapy compared to the $CXCR4^{low}$ NSCLC tissues

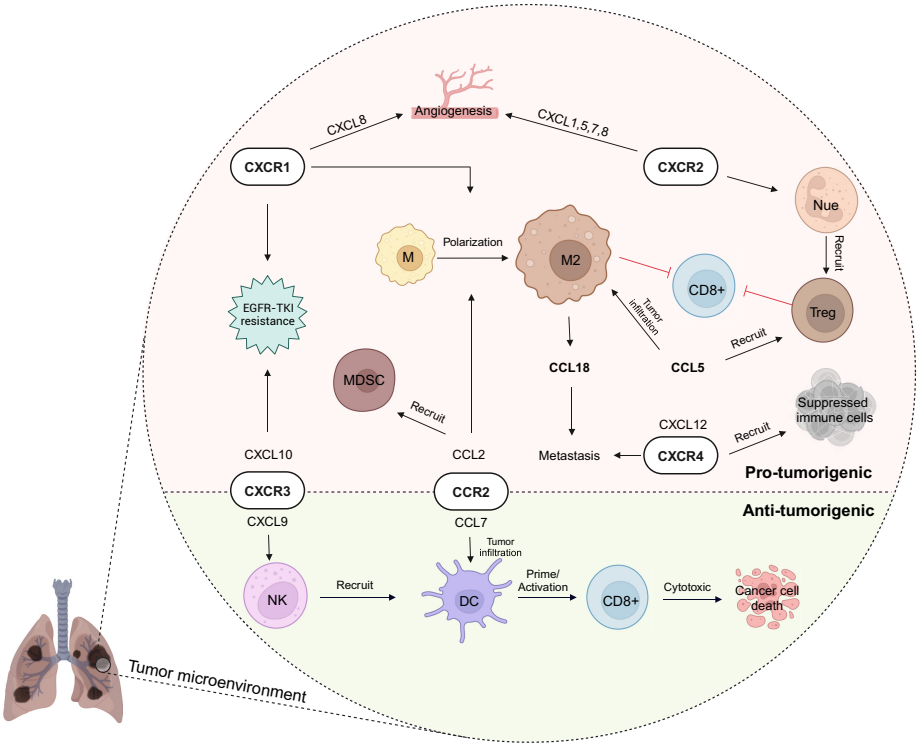

FIGURE 3
Chemokine network in lung cancer immunity. In lung cancer's tumor microenvironment (TME), chemokines play a dual role, fostering both anti-tumor immunity and pro-tumorigenic activities (e.g., CXCR3 and CCR2 involvement with cytotoxic activity by natural killer (NK) cell - dendritic cell (DC) -T cells as well as immunosuppressive activity). Immunoregulatory cells like M2 macrophage, regulatory T (Treg) cell, and myeloid-derived suppressor cell (MDSC) are recruited by chemokines to the TME, creating an immunosuppressive environment. Meanwhile, CXCR1 and CXCR2 contribute to pro-tumorigenic angiogenesis, supporting cancer growth and migration to other organs. These complexities highlight the need for targeted approaches to modulate immune responses effectively in lung cancer. EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; M, macrophage; Nue, neutrophil. Created with BioRender.com.

(153). Furthermore, the CXCR4 antagonists suppressed the growth of lung cancer growth: Peptide R prevented the recruitment of metastasis-initiating cells and inflammatory monocytes toward CXCL12-enriched sites (69) and AMD3100 reduced the progression of cancer in orthotopic SCLC mouse model (155).

Another critical chemokine axis is the CCL2-CCR2 pathway, which contributes to the polarization of macrophages toward an M2 phenotype. Tumor macrophage infiltration and CCR2 expression have been found to correlate with both tumor stage and metastasis in human lung cancer samples (156). Decreased expression of CCL2 in human SCLC (157) and blockage of CCL2 in a mouse lung cancer model (158) showed lower macrophage infiltration of tumors with a reduction in M2 polarization and, as a consequence, an increase in $CD8^+$ T cell activation. Therapeutic CCL2-blockade also decreased the recruitment of MDSCs in both the blood and tumors collected from lung cancer-bearing mice (159) and resulted in increased $CD4^+$ and $CD8^+$ T cell infiltration of tumors, higher production of IFNγ, and improved survival of tumor-bearing mice. These effects were even more pronounced when combined with PD-1-specific ICI therapy.

CCL7, another ligand of CCR2, has been studied in depth in solid tumors. Although high CCL7 expression in colorectal (160, 161), breast (162), and uterine (163) cancer is known to promote metastasis and suppress tumor immunity, the expression of CCL7 in NSCLC has been shown to be anti-tumorigenic (164). CCL7 is highly expressed by NSCLC tumors and positively correlated with cDC1 infiltration and overall survival in NSCLC patients. In LUAD mouse models, alveolar macrophage-derived CCL7 increased infiltration of cDC1s into the TME and potentiated the proliferation of intra-tumoral T cells. Similarly, CCL7 administration prolonged the survival of mice with lung cancer and enhanced the efficacy of PD-1 ICI. This study is consistent with the idea that chemokines may have different roles in different types of cancer and suggests that CCL7 has the potential to be an adjuvant in immune checkpoint therapy for lung cancer (165).

Secretion of CCL5, a ligand for CCR3, CCR5, and CCR1 (80), was markedly increased in mouse lung cancers harboring oncogenic EGFR and KRAS mutations (166). CCL5 deficiency in KRAS mutant LUAD resulted in a decrease in Treg cells and reduced lung tumor burden, indicating that the production of CCL5 by tumor cells contributes to an immunosuppressive environment in the lung. Additionally, high expression of CCL5 was associated with a negative prognosis, Treg cell recruitment, and altered CD8 effector function in LUAD patients. Consistent with this study, the spatial transcriptomic profiles of NSCLC showed upregulation of CCL5 in tumors with high infiltration of $CD163^+$ TAMs (167).

Another chemokine associated with poor survival in NSCLC is CCL18, a ligand for the PITPNM3, GPR30, and CCR8 receptors (168). In lung cancer, TAM-derived CCL18 is thought to promote metastasis by facilitating the migration of lung cancer cells (169). Compared to healthy controls, NSCLC patients had higher serum CCL18 concentrations, which were also associated with poor survival (170). Further, local CCL18 concentrations were higher in lymph node-positive NSCLC patients (171), suggesting that CCL18 could potentially be used as an independent diagnostic marker in metastatic NSCLC (172). In addition to CCL18, CXCL12 and CCL22 are known to alter the TME in lung cancer by modulating TAM activity (56, 173).

Overall, CXCR2, CXCR4, CCR2 are currently the most extensively studied chemokine receptors in NSCLC and are considered potential biomarkers for lung cancer (Table 1). These chemokine receptors show promise as therapeutics, especially when combined with ICI, as demonstrated in several studies (147–150, 164, 165). The lung is not only a primary tumor site but also a common site for metastasis. Thus, the therapeutic use of chemokines to prevent lung tumors and metastasis would be a positive direction for future cancer research and could potentially offer treatment options for patients who have failed more traditional therapies.

4.2 Clinical trials using chemokine-related therapies in lung cancer

Due to the intricate and diverse characteristics of chemokines, the selection of the appropriate target and therapeutic approach is paramount. Currently, most studies on chemokine therapy remain in the preclinical stage, yet some clinical trials have been undertaken utilizing various chemokine systems and approaches (Table 2). For instance, combinations of chemokines for effective immunotherapy are being studied in several clinical trials. There is one Phase I study that engineered anti-glypican-3-CAR-T cells to secrete IL-7 and CCL19 (anti-GPC3–7 × 19 CAR-T) for enhancing the expansion and migration in solid tumors (NCT03198546). In patients with advanced hepatocellular carcinoma, tumors completely disappeared following intratumoral injection of anti-GPC3–7 × 19 CAR-T (174). This study is planned to perform the similar clinical trial on LUSC with the GPC3 expression (NCT03198546). Another Phase IIa trial assessed the efficacy of BMS-813160 (CCR2/5 inhibitor) administered with nivolumab, a PD-1 inhibitor (NCT04123379). In 14 patients with NSCLC, BMS-813160 was co-administered with nivolumab prior to resection, but did not significantly improve the efficacy of the nivolumab treatment (175). In the other Phase I clinical trial (NCT02946671), 12 NSCLC

TABLE 1 Pre-clinical studies about chemokine in lung cancer immunity.

Chemokine		Molecule	Cancer Type	Property	Immune cells involved	Reference
Receptor	Ligand					
CXCR1		EGFR-TKI	NSCLC	Pro-tumorigenic	Neu, M2	(144)
CXCR2			NSCLC	Pro-tumorigenic	Neu, $CD8^+$ T, NK	(147)
	CXCL8		Lung cancer	Anti-tumorigenic	Neu, CD8+T	(148)
			LUSC	Pro-tumorigenic	Neu	(149)
	CXCL1		NSCLC	Pro-tumorigenic	Treg	(150)
CXCR3	CXCL10		Lung cancer	Anti-tumorigenic	CD8+T, NK	(151)
	CXCL10	EGFR-TKI	Lung cancer	Pro-tumorigenic		(152)
CXCR4			NSCLC	Pro-tumorigenic	Increased immune checkpoint expression	(153)
	CXCL12	Peptide R	Lung cancer	Pro-tumorigenic	Monocyte	(69)
	CXCL12	AMD3100	SCLC	Pro-tumorigenic		(155)
	CXCL12		Lung cancer	Pro-tumorigenic	TAM	(173)
CCR2	CCL2		Lung cancer	Pro-tumorigenic	M2, CD8+T	(156–158)
		ICI	Lung cancer	Pro-tumorigenic	MDSC, CD4+T, CD8+T	(159)
	CCL7	ICI	NSCLC	Anti-tumorigenic	DC, Alveolar M, T	(164)
		ICI	NSCLC	Anti-tumorigenic	DC, T	(165)
	CCL5		LUAD	Pro-tumorigenic	Treg, CD8+T	(166)
			NSCLC	Pro-tumorigenic	TAM	(167)
	CCL18		NSCLC	Pro-tumorigenic	TAM	(169)
	CCL22		Lung cancer	Pro-tumorigenic	TAM	(56)

TABLE 2 Clinical trials involving chemokines in lung cancer.

Targeted Chomokine	Molecule	Cancer Type	Phase	Status	Identifier
CCR2/5	BMX-813160 (CCR2/5-inhibitor), BMS-986253 (anti-IL-8), nivolumab	NSCLC, hepatocellular carcinoma	II	Completed	NCT04123379
CCR4	mogamulizumab (anti-human CCR4 monoclonal antibody) + nivolumab	lung, gastric, esophageal, renal, and oral cancer	I	Completed	NCT02946671
CCR8	BAY 3375968 (anti-CCR8 antibody) + pembrolizumab	lung, breast, head and neck cancer, and melanoma	I	Recruiting	NCT05537740
CXCR1/2	SX-682 (CXCR1/2 inhibitor) + pembrolizumab	NSCLC	II	Recruiting	NCT05570825
CXCR4	LY2510924 (peptide CXCR4 antagonist)	SCLC	II	Completed	NCT01439568
	212-Lead Pentixather (CXCR4-targeted ligand)	lung carcinoid tumor, SCLC, neuroendocrine tumor of the lung	I	Not yet recruiting	NCT05557708
CXCR5	CXCR5 modified EGFR CAR-T cells	NSCLC	I	Recruiting	NCT05060796
CX3CR1	$CX3CR1^+$ $CD8^+$ T cells	NSCLC	Principal Test	Active	NCT06054152
CCL19	GPC3/TGFβ-CART cells secreting IL7/CCL19 and/or SCFVs	squamous cell lung cancer, hepatocellular carcinoma	I	Recruiting	NCT03198546
CCL21	Autologous dendritic cell adenovirus CCL21 vaccine	NSCLC	I	Completed	NCT00601094
				Terminated	NCT01574222
				Active	NCT03546361
	GM.CD40L Vaccine With CCL21	lung cancer, adenocarcinoma	I, II	Completed	NCT01433172
CXCL12	CLG (CXCL12 loaded aqueous gel)	solid tumors (lung, endometrium, kidney, glioblastoma, colorectal, and ovary)	Principal Test	Active	NCT05818865

Clinical trials recruiting lung cancer patients for each chemokine receptor and ligand were searched from ClinicalTrials.gov records.

patients administered mogamulizumab, a humanized anti-human CCR4 monoclonal antibody (176). This study exhibited selective depletion of activated Tregs in peripheral blood mononuclear cells and indicated potential immune response induction by mogamulizumab, suggesting this antibody could be used in combination with other immunotherapies to enhance patients' outcomes. Additionally, two clinical trials employing DC vaccines have been conducted. One Phase I study utilized a CCL21-overexpressing DC vaccine intratumorally in lung cancer patients (NCT01574222) (177). This therapy elicited systemic tumor-antigen-specific immune attack, enhanced tumor infiltration by cytotoxic T cells, and increased PD-L1 expression by tumor cells. Whether PD-L1 upregulation would enhance the effectiveness of PD-1/PD-L1 ICI therapy remains to be evaluated. Another Phase I/ randomized Phase II study (NCT01433172) in NSCLC patients compared the GM.CDL vaccine, which recruits and activates DC alone and in combination with CCL21 (178). Although the addition of CCL21 did not yield significant therapeutic benefits overall, it showed promise in one patient with remarkable tumor lymphocyte infiltration, prompting further investigation of CCL21 in combination therapies. Meanwhile, there are studies utilizing chemokines as biomarkers. Early after initiation of anti-PD-1 therapy, an increase in the frequency of the circulating $CX3CR1^+$ $CD8^+$ T cells is associated with improved response and survival in NSCLC patients (179). Closely related to this study is an ongoing observational trial (NCT06054152) using $CX3CR1^+$ $CD8^+$ T as a predictor of immunotherapy efficacy for NSCLC patients. CXCR4 is valuable as a diagnostic biomarker, enabling the potential for CXCR4-directed molecular imaging and therapy (180) and the related Phase I study (NCT05557708) has been planned. An exploratory analysis of a phase II study (NCT01439568) (181) assessed the utility of CXCR4 expression in circulating tumor cells as a prognostic biomarker in 89 lung cancer patients (61, 62, 136, 139). This study indicated that positive CXCR4 expression in lung cancer tissue did not significantly impact survival prognosis, highlighting the complexities of utilizing chemokines as standalone therapies in clinical settings despite promising preclinical results in cancer research.

5 Conclusion

The advent of cancer immunotherapy has marked a revolutionary shift in cancer treatment, offering a targeted approach to eliminating cancerous tissue while potentially mitigating the adverse effects associated with traditional chemotherapy. This breakthrough has stimulated optimism for both preventing and treating metastatic cancer. However, the TME presents a formidable obstacle, acting as a protective barrier that hampers the efficacy of immunotherapy. Current research endeavors are dedicated to overcoming the

challenges posed by immunosuppression and physical barriers within the TME. Chemokines have emerged as pivotal players in augmenting the effectiveness of cancer immunotherapy, orchestrating immune cell signaling within the TME, and facilitating their migration toward cancer cells. Moreover, these chemokines hold promise as valuable biomarkers for prognostication and treatment guidance. Despite abundant preclinical studies, there is a notable scarcity of clinical investigations, likely attributed to the complexity of chemokines and the inherent difficulties in developing them as viable therapeutic agents.

Nevertheless, numerous studies conducted on lung cancer patients underscore the potential of targeting chemokine axes as a promising therapeutic strategy (Tables 1, 2). CXCR2 and CCR2 are the most extensively studied chemokine receptors in preclinical studies of lung cancer. Given that lung tissue is a common site of primary lung cancer development as well as metastasis from tumors outside the lungs, treatments using chemokines such as CXCR4 appear promising. The use of chemokine-related therapies in combination to increase the efficacy of conventional immunotherapy is also being explored in both preclinical and clinical studies, offering promising prospects for enhancing the efficacy of cancer immunotherapy in the future.

Author contributions

SP: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. HJ: Conceptualization, Validation, Visualization, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA034196 to SP and by unrestricted funds from the Jackson Laboratory for Genomic Medicine to SP.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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