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Macrophage chemoattractants secreted by cancer cells: Sculptors of the tumor microenvironment and another crucial piece of the cancer secretome as a therapeutic target

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ABSTRACT

Beyond their essential role in leukocyte homing in the context of inflammation, chemokines orchestrate the host response to cancer progression. Chemokines are key accelerators in the amplification of inflammatory signals and metastasis in the distal zone of tumors, indicating possible immune editing of tumor cells in the microenvironment. This review summarizes the main macrophage-attracting chemokines secreted from cancer cells and how these mediators can be targeted to improve cancer immunotherapy in multiple cancer types.

1. Introduction

Macrophages comprise the main immune cell population in the tumor stroma. Based on their function, macrophages have been classified as classical M1 and alternative M2 polarized subtypes. When a tumor starts to develop, anti-tumoral M1 macrophages attack to block its growth [1]. With tumor growth, tumor cells can reprogram macrophages and convert them into tumor-associated macrophages (TAMs) [2].

Several factors induce this macrophage fate change. For example, high glycolysis in tumor cells leads to increased lactic acid in the microenvironment, which after uptake by TAMs, can induce the pro-tumoral M2-like transcriptional program [2]. M2 macrophages show divergent functions such as immunosuppression, angiogenesis and matrix remodeling [3]. On the other hand, anti-tumoral M1 polarization is stimulated by Interferon regulatory factor 3 (IRF3), Interferon Regulatory Factor 5 (IRF5), STAT1, and STAT5, while Interferon Regulatory Factor 4 (IRF4), STAT3, and STAT6 contribute M2 activation signals [3]. Targeting and reprogramming of tumor-associated macrophages by antibodies have attracted recent attention to alter macrophage polarization in tumor growth and metastasis [4,5].

Chemokines secreted by cancer cells also affect macrophage polarization and are critical modulators of the tumor microenvironment [3]. Chemokines independently modulate tumor growth, induce trafficking of leukocytes into the tumor microenvironment, and indirectly induce the tumor-associated stromal compartment to secrete angiogenic and lymphangiogenic growth factors. These effects shape the tumor inflammatory milieu and regulate the balance between anti-tumoral and pro-tumoral factors [6,7]. Besides, chemokine signaling utilizes G-protein coupled receptor pathways, presenting numerous potential targets for intervention [8].

2. Monocyte/macrophage chemoattractants

Tumor promotion of suppression by chemokines demonstrates that there is a balance between anti- and pro-tumoral activities of the inflammatory cells. Tumor-associated macrophages (TAMs) are attracted into tumor sites by chemoattractants such as CCL2, CCL3, CCL4, CCL5, CCL7, CCL8 and CXCL12 [9] (Fig. 1). These macrophages then undergo differentiation in the tumor microenvironment, depending on the inflammatory context, into anti-tumoral (M1) or pro-tumoral (M2) macrophages.

Abbreviations: 5-FU, 5-Fluorouracil; Akt, Protein Kinase B; CCL, CC chemokine ligand; CCR, CC chemokine receptor; CcRCC, clear cell renal cell carcinoma; CML, chronic myeloid leukemia; CRC, colorectal cancer; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor; ELR, N-terminal ELR (Glu–Leu–Arg) amino acid motif (in CXC chemokines); ER, estrogen receptor; HCC, hepatocellular Carcinoma; HER2, human epidermal growth factor 2; HNSCC, head and neck squamous cell carcinoma; MDSCs, myeloid derived suppressor cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TAM, tumor-associated macrophages; TOPK, T-LAK cell-originated protein kinase; VEGF-A, vascular endothelial growth factor-A; VEGF-C, vascular endothelial growth factor-C

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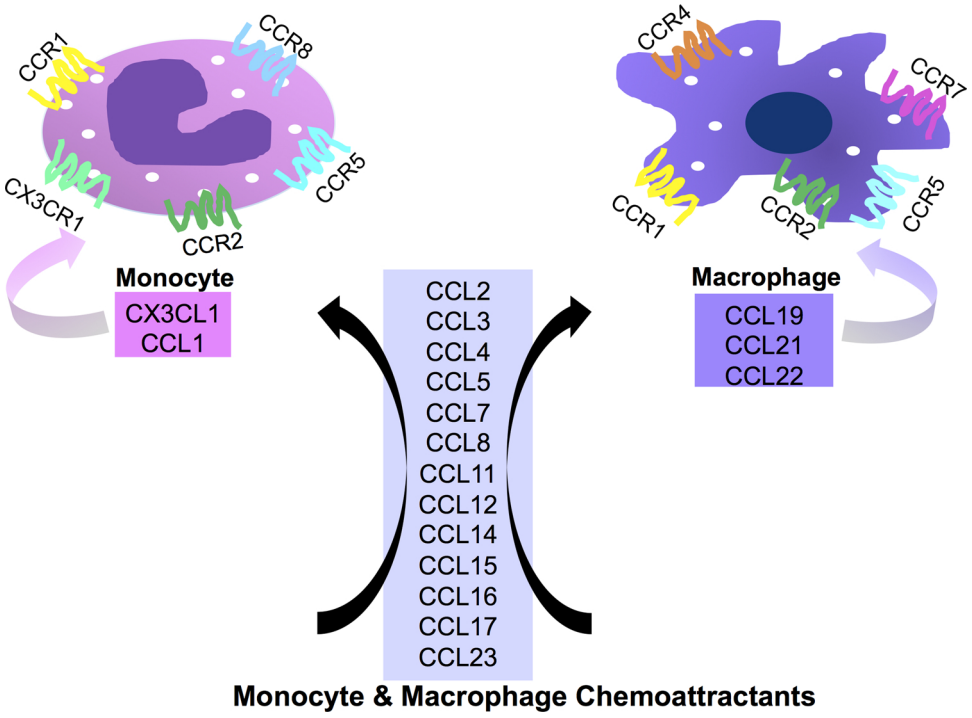

Fig. 1. Schematic demonstration of CCL- and CXCL- type monocyte/macrophage chemoattractants.

M1 and M2 macrophages are recruited to the inflammatory tissues in a phase-dependent fashion. The initial phase, associated with M1 macrophages (IL-12^{high}, IL-10^{low}, and IL-23^{high}), is followed by recruitment of M2 macrophages (IL-12^{low}, IL-10^{high}, and IL-23^{low}). M1 macrophages can be converted into M2 macrophages during the period of resolution, depending on the inflammatory factors [10,11].

Different chemokines can shift the recruitment of M1 and M2 type macrophages. CXCL9-11, chemokines induced by Type I and Type II Interferon, have converted macrophages into the M1 type. CCL19, CCL21, CCL24, CCL25, CXCL8, CXCL10 and XCL2 have been shown to induce M1 macrophage chemotaxis in a dose dependent fashion. Some chemokines, for instance CCL7 and CXCL8 can induce both M1 and M2 macrophage chemotaxis [11].

3. Tumor derived monocyte/macrophage chemoattractants sculpting the tumor microenvironment

Cancer cells release mediators such as cytokines, chemokines, and exosomes that can promote tumor progression and metastasis. Chemokines secreted by cancer cells promote tumor progression as growth factors, chemoattractants for pro-tumoral immune cells into the inflammatory area, and boosters for metastatic seed cells. Many types of cancer have been found to secrete a variety of CCL- and CXCL-type chemokines [12] (Fig. 2). These chemokines as chemopreventive biomarkers are possible therapeutic targets in cancer.

3.1. CCL-type chemokines secreted by cancer cells

CCL-type inflammatory cytokines include CCL1-5 [13]. CCL2-mediated macrophage chemotaxis has been shown to stimulate cancer progression and metastasis in breast, ovarian and prostate cancer. ER$^+$ breast cancer patients have been shown to elevate levels of CCL2 and CCL5, which is associated with infiltration of tumor-associated macrophages [14]. CCL2 also promotes metastasis in prostate cancer via promoting prostate cancer extravasation into the bone microenvironment and inducing osteoclast activity in tumor-induced bone lesions [15]. In colorectal cancer, Pyruvate kinase muscle isozyme M2-mediated CCL2 induces pro-tumoral (M2) macrophage recruitment in the tumor microenvironment [16]. CCL2 expression is upregulated in head and neck squamous cell carcinoma (HNSCC) when compared with normal mucosa. Besides, primary tumor macrophage content is strongly associated with lymph node metastasis in HNSCC [17]. In spite of its stimulation of pro-tumoral macrophage recruitment, loss of CCL2 was shown to augment breast cancer progression in the early phase of the disease through decreased tumor cell killing by tumor-entrained neutrophils, suggesting anti-tumor role for CCL2 in early stages of tumor progression [18]. CCL2 generated by non-tumor cells within the tumor microenvironment of glioblastoma multiforme is required for recruiting both immunosuppressive CCR4$^+$ Treg cells and CCR2$^+$Ly6C$^+$ monocytic myeloid derived suppressor cells [19].

CCL3 expressed by oral squamous cell carcinoma cells contributes to cancer progression by inducing leukocyte accumulation, angiogenic pathways, and eosinophilic infiltration [20]. In chronic lymphocytic leukemia, CCL3 alters the lymph node microenvironment by increasing CD3$^+$ T cell and CD57$^+$ cells [21].

CCL5 maintains tumor cell proliferation, induces Treg, CD4 T cells, and mediates monocyte recruitment and tumor cell spread to distant organs through neoangiogenesis and bone metastasis. It augments MMP-3-mediated cell migration and VEGF-A-dependent tumor angiogenesis in human chondrosarcoma [22–24]. Furthermore, CCL5 stimulates lymphangiogenesis through VEGF-C production in human chondrosarcoma cells [25]. Increased levels of CCL5 and its receptor have been found in more than 58% of basal and HER2$^+$ subtype breast cancer patients and is a critical factor in estrogen-dependent breast cancer progression [26]. CCL5 stimulates proliferation of pancreatic cancer cell through increasing F-actin polymerization, which seemingly is a potential marker for aggressive pancreatic cancer [27]. Additionally, CXCL5 levels have been reported to be elevated in stages III and IV of ovarian cancer as compared to stages I and II [28]. It has been shown that NSCLC cells also express CCL5, but its levels are not correlated with macrophage chemotaxis. It has emerged as a predictor of survival in Stage I Lung adenocarcinoma [29], supporting different roles of CCL5 in the early and late stage of different cancer types.

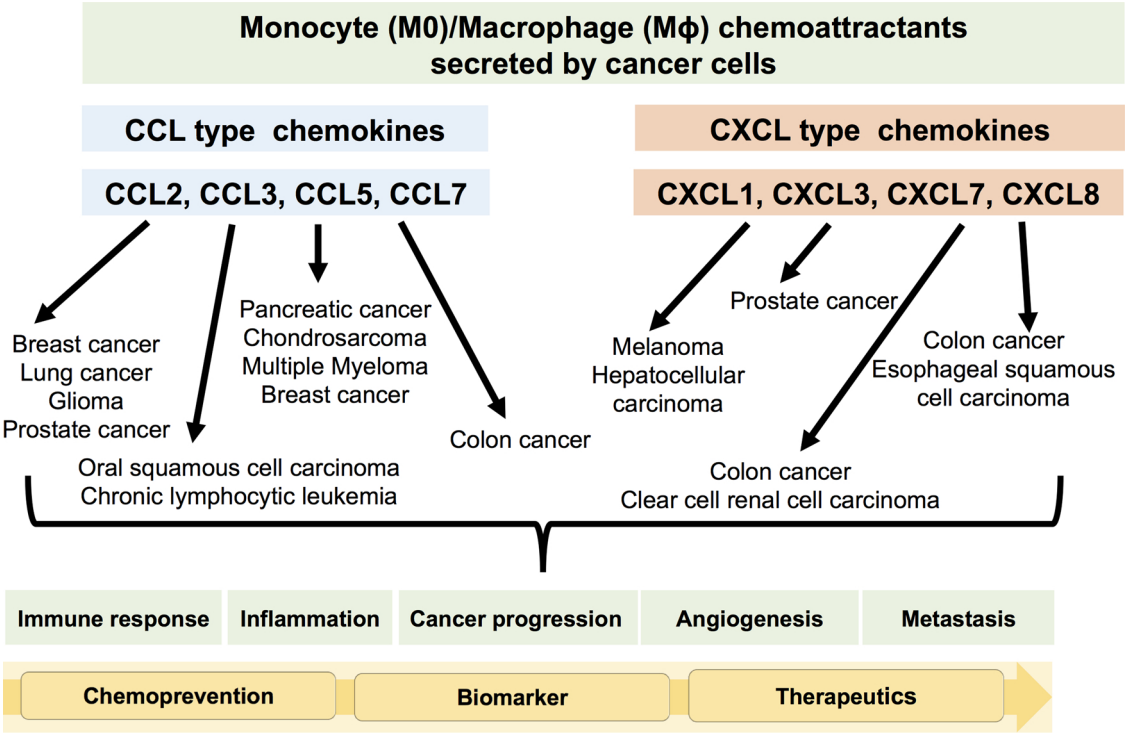

Fig. 2. Monocyte (M0)/Macrophage (MΦ) chemoattractants secreted by various types of cancer.

3.2. CXCL-type chemokines secreted by cancer cells

CXC chemokines (CXCL1-14) contain the ELR motif and interact with CXCR1 and CXCR2 receptors. They have been shown to exhibit angiogenic or angiostatic activity [30]. CXCL1 was first isolated from human melanoma-conditioned medium. In melanoma cells, CXCL1 can be induced by pro-inflammatory signals such as IL-1β and TNF-α during inflammation [31]. Overexpression of CXCL1 is associated with constitutive NF-κβ activation [32]. CXCL1 has also found to be elevated in antibody array-based assays performed to evaluate the secretome from a non-contact co-culture system with hepatocellular carcinoma cells and macrophages [33].

Cancer cells can reshape chemokine expression profile to promote migration of a variety of immunosuppressive cells including tumor-associated macrophages (TAMs) and MDSCs [9]. CXCL2 and MIF are elevated in tissues of patients with bladder cancer, and these elevated levels are correlated with an increased number of tumor-associated $CD33^+$ MDSCs [34]. When M2 macrophages and HCC cells were co-cultured, CXCL2 was significantly elevated. In addition, its expression was found significantly higher in tumor tissues as compared to the normal tissues from HCC patients, indicating that it could promote HCC metastasis [35]. Treatment of prostate cancer cells with exogenous CXCL3 promotes migration of cancer cells and immortalized prostate epithelial cells along with regulating prostate cancer related genes [36].

Colon cancer cells upregulate CXCL4 to acquire growth advantage after 5-FU chemotherapy in a murine colon cancer model established with CT26 cells. Results from the animal model indicate that elevated CXC-type chemokines may be a predictive marker for poor outcome as observed in patients with colon cancer treated by neoadjuvant chemotherapy [37].

The CXCL7 /CXCR2 axis is critical in colorectal cancer development, and its receptor CXCR2 expressions are higher in liver metastasis in these colon cancer subjects [38]. Circulating levels of CXCL7 may serve as a predictive marker for efficacy of sunitinib, an antiangiogenic agent, in patients with ccRCC [39].

CXCL8 is associated with tumor growth in lung, colorectal (CRC), breast, prostate, melanoma, pancreatic and liver cancer [40]. CXCL8-mediated resistance to anoikis, described as programmed cell death stimulated by reduction of correct cell/ECM attachment, is associated with the increase of TOPK and the activation of AKT and ERK pathways in CRC cells [41]. CXCL8 can alter CCL2 expression on prostate cancer cells autonomously and regulate CXCL12 secretion by tumor-associated macrophages in a paracrine manner [42]. Paclitaxel, a chemotherapeutic agent, erlotinib, and a topoisomerase inhibitor, camptothecin increase CXCL8 expression in lung and prostate cancer cells at both transcriptional and translational levels, indicating that CXCL8 could be beneficial as a biomarker for prognosis and drug efficacy [43].

4. Targeting of CCL/CXCL type chemokines secreted by cancer cells

Chemokines are key regulators, which could be modulated in order to improve the efficiency of cancer immunotherapy. Numerous therapeutic approaches have been proposed, including intra-tumoral delivery of chemokines (CCL1, CCL3, CCL5, CCL22 and CXCL1), transducing chemokine receptors, blocking chemokine/chemokine receptors, and targeting posttranslational modification of chemokines [44] (Fig. 3).

CCL2 by neutralizing anti-CCL2 monoclonal antibodies can reduce central nervous system (CNS) tumor infiltration of TAMs and MDSCs in mice bearing glioma, suggesting that targeting tumor-derived CCL2 diminishes the accumulation of these immunosuppressive cells [45]. Intratumoral nitration/nitrosylation of CCL2 in different cancers prevent T cell infiltration. A new agent, AT38, which interferes with the production of reactive nitrogen species, induces substantial intratumoral T-cell infiltration [46]. Targeting CCL2 by monoclonal antibodies inhibits breast cancer metastasis to the lung niche [47]. Combinational therapy containing CCL2 antibody plus standard chemotherapy is currently under investigation for prostate and ovarian cancer [47,48]. In chondrosarcoma, miR-507/VEGF-C signaling was detected in tumor lymphangiogenesis via CCL5, suggesting targeting both CCL5 and VEGF-C pathways should be considered as a potential therapeutic strategy [25].

CCL2, CCL3, and CCL5 chemokines have binding affinity for CCR1,

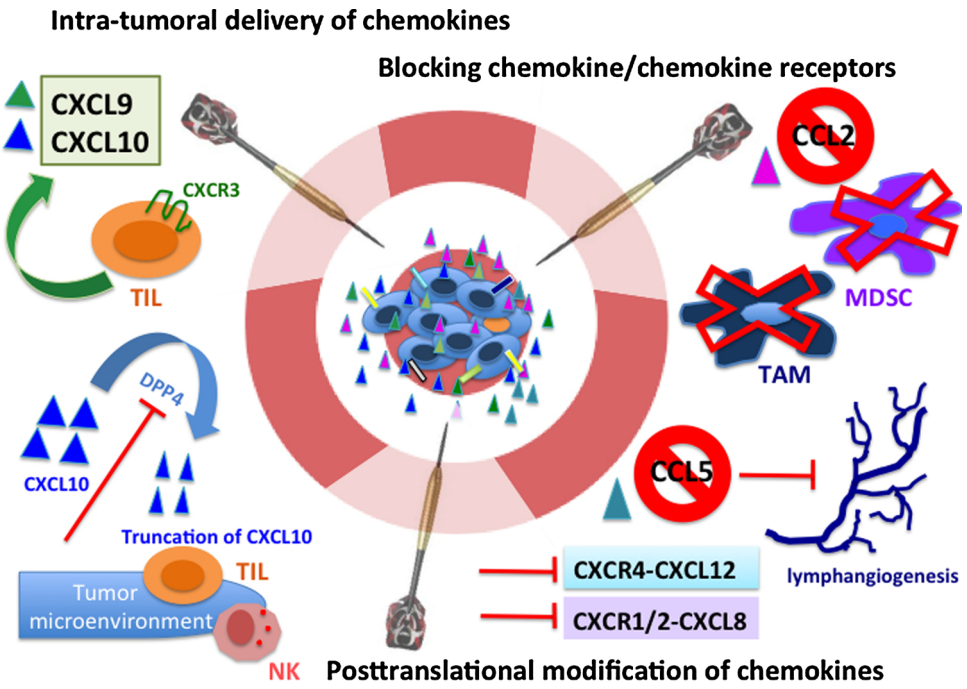

Fig. 3. Therapeutic approaches for targeting of CCL/CXCL type chemokines secreted by cancer cells.

Table 1
Clinical trials registered at ClinicalTrials.gov targeting macrophage chemoattractants derived from cancer cells and their receptors.

Drug type	Drug target	Cancer type	Study Status (completed/ on-going)	Clinical Trial Identification
Carlumab/ CNTO 888	CCL2	Prostate cancer	completed	NCT00992186
		Solid tumors	completed	NCT01204996
HuMax-IL8	IL8/ CXCL8	Solid tumors	completed	NCT02536469
MLN1202	CCR2	Metastatic cancer	completed	NCT01015560
CCX872-B		Pancreatic cancer	on-going	NCT03778879
Maraviroc	CCR5	Metastatic colorectal cancer	completed	NCT01736813
BMS-813160	CCR2/ CCR5	Pancreatic Ductal Adenocarcinoma	on-going	NCT03767582
SX-682	CXCR1/ CXCR2	Metastatic melanoma	on-going	NCT03161431
AZD5069	CXCR2	Metastatic prostate cancer	on-going	NCT03177187

CCR2, CCR3, and CCR5 [49]. A phase Ib trial of a CCR2 antagonist (CCX872) [50] and a phase II trial of CCR monoclonal antibody (MLN1202) [51] will be yield more data about the effects of blocking these pathways in patients with cancer bone metastasis from solid tumors. CCL5 and CCL5/CCR5 interaction have been targeted by CCR5 antagonists [52], inhibition of CCL5 secretion by administration of chemotherapeutic agents such as a PI3Kδ inhibitor [53], zoledronic acid [54], and blocking crosstalk between cancer cells and mesenchymal stem cells through the EGFR inhibitor, gefitinib [55]. Another chemokine receptor CXCR4, a receptor for CXCL12, has been targeted in a clinical trial to investigate the safety of combinational immunotherapy with a CXCR4 peptide antagonist (LY2510924) and a PD-L1 antibody, durvalumab [56]. In preclinical studies, ABX-CXCL8 and HuMax-CXCL8, neutralizing antibodies against CXCL8, target CXCL8-CXCR1/2 pathway. A phase Ib pilot study with HuMax-CXCL8 has been focused on patients with metastatic or unresectable solid tumors (Clinical trial identification: NCT02536469) [57]. A brief list with the completed and on-going clinical trials targeting macrophage chemoattractants derived from cancer cells and their receptors can be found in Table 1.

Another aspect of targeting chemokines in cancer immunotherapy is to utilize the immune modulatory effect of CXCL9 and CXCL10 within a tumor site for promoting anti-tumor immunity. This has been seen in several solid tumors including lung, colon, kidney and melanoma, where it is exerted by tumor suppressive $CXCR3^+$ tumor infiltrating lymphocytes and natural killer cells [58]. Increased expression of tumor-derived CXCL10 is associated with favorable prognosis, indicating that the possible development of a personalized therapy based on CXCL10 would be promising [59]. The maintenance of a full length biological form of CXCL10 through dipeptidyl peptidase-4 (DPP4) inhibition enhances the recruitment of lymphocytes into the tumor parenchyma and boosts immune checkpoint blockades in a melanoma model [60,61]. Combination of CXCL9 gene therapy with low-dose cisplatin increases therapeutic efficacy against colon (CT26) and Lewis lung carcinoma (LL/2c) murine models [62].

5. Clinical significance & perspective

Chemokines and chemokine receptors play key roles in chemoprevention, diagnosis, cancer progression and metastasis. Profiling chemokines and evaluation of chemokine/chemokine receptor axis status followed by chemotherapy drugs could be insightful for describing an anti-tumoral immune response and elucidating specific intra-tumoral leukocytes in the tumor milieu. Selective chemokine/chemokine receptor inhibitors have been developed to enhance the responsiveness of immune checkpoint inhibitors. Development of new potential therapeutic agents targeting both pro-tumoral and anti-tumoral activities of chemokines secreted from cancer cells could pave the way to improved survival outcome.

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Conflicts of interest

The author declares no conflict of interest.

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