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Targeting CXCL12/CXCR4 Axis in Tumor Immunotherapy

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Abstract

Chemokines, which have chemotactic abilities, are comprised of a family of small cytokines with 8–10 kilodaltons. Chemokines work in immune cells by trafficking and regulating cell proliferation, migration, activation, differentiation, and homing. CXCR-4 is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1, also known as CXCL12), which has been found to be expressed in more than 23 different types of cancers. Recently, the SDF-1/CXCR-4 signaling pathway has emerged as a potential therapeutic target for human tumor because of its critical role in tumor initiation and progression by activating multiple signaling pathways, such as ERK1/2, ras, p38 MAPK, PLC/ MAPK, and SAPK/ JNK, as well as regulating cancer stem cells. CXCL12/CXCR4 antagonists have been produced, which have shown encouraging results in anti-cancer activity. Here, we provide a brief overview of the CXCL12/CXCR4 axis as a molecular target for cancer treatment. We also review the potential utility of targeting CXCL12/CXCR4 axis in combination of immunotherapy and/or chemotherapy based on up-to-date literature and ongoing research progress.

Keywords

Cancer; cancer stem cell; immunotherapy; CXCR4; CXCL12; chemokine

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CONFLICT OF INTEREST

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1. INTRODUCTION

Chemokines play active roles in embryogenesis, hematopoiesis, mitogenicity, and innate and adaptive immunity [1–6]. Chemokines consist of CXC, CC, C or CX3C subtypes depending on different cysteine residues at the N-terminus [7–9]. Chemokines bind and subsequently activate receptors such as G-protein-coupled receptors (GPCR), chemotactically guide immune cells to specific locations [4, 10–11]. Over 50 individual chemokines [4] and their corresponding receptors [10] have been identified. Recently, the alpha-chemokine receptor, C-X-C chemokine receptor type 4 (CXCR4) and its ligand, the alpha-chemokine CXCL12, have been found as the most widely expressed in tumors and implicated in cell proliferation, migration, and tumor metastasis. Importantly, the CXCL12/CXCR4 axis has emerged as a drug target for human tumor owing to its crucial role in promoting and maintaining cancer stem cells (CSC). In this review, our current understanding of the oncogenic roles of CXCL12/CXCR4 will be summarized and discussed with regards to its therapeutic potential as drug target.

CXCL12 is widely expressed in various human tissues, including liver, lungs, bone marrow, lymph nodes, stromal and endothelial cells [12–14]. Besides CXCR4, CXCR7 has also been found to bind to CXCL12 with high affinity [15–16]. CXCR7 is now classified as a chemokine co-receptor, together with CXCR4, for CXCL12 and C-X-C motif chemokine I-TAC (CXCL11)[17–18]. Similar to CXCL12, CXCR4 is also widely detected in the central nervous systems, neural stem cells, liver oval/stem cells, CD34+ hematopoietic progenitor cells, white blood cells [19], primordial germ cells, skeletal muscle satellite progenitor cells, as well as intestinal epithelium [20]. The ubiquitously present CXCL12/CXCR4 axis highlights its essential roles in various physiological processes [21], homeostasis and trafficking of immune cells [22].

CXCL12/CXCR4 axis activates various signaling pathways that promote chemotaxis, adhesion and migration, cell proliferation and survival [23]. PI3 kinase, Ras, stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), phospholipase C (PLC)/mitogen-activated protein kinase (MAPK), p38 MAPK and AKT are all downstream effectors of CXCL12/CXCR4 axis, through which tumor cell growth, dissemination and migration are facilitated [24–29].

CXCR4 can be activated in different ways in tumor cells. First, hypoxia can up-regulate CXCR4 signaling [30]. Second, Wnt/beta-catenin can also positively regulate CXCR4 expression [31]. Third, NF-κB can also activate CXCR4 expression. Upon ligand induction, NF-κB subunits of p50 and p65 bind to the CXCR4 promoter, where a NF-κB binding site, transcriptionally activating CXCR4 and stimulating tumor invasion [32–37].

CXCR4 pathway has been implicated in the SHH-GLI1-NANOG network [38], Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) [39–40], phosphoinositide 3-kinase (PI3K)/AKT [41–42] and NF-κB57 [37, 43]. In turn, the CXCL12/ CXCR4 signaling activates MAPKs signaling which stimulates chemotaxis and cell proliferation [41, 44], induces PLC/PKC-Ca^{2+} signaling and affects PI3K/AKT, and promotes cell migration and survival [41–42]. This phenomenon suggests a feedback loop between CXCR4 and the other

signaling pathways. CXCL12/CXCR4 signaling pathway may transactivate HER2-neu to stimulate invasive and metastatic signals of breast [45–46], esophageal [47], lung [48], prostate [49], as well as ovarian cancers [50].

CXCR4 protein is also activated through several post-transcriptional levels. Sustained exposure of cells to CXCL12 desensitizes them to CXCL12 through the mechanism of endocytosis of CXCR4. The receptor is ubiquitinated and simulates the CXCR4 to endosome and degrades it in lysosomes [51]. Activated YY1, a transcription factor, can inhibit expression of CXCR4 through the phosphorylation of carboxyl-terminal Src kinase homologous kinase in breast cancer cells [52–53]. Histone deacetylase 3-interacting protein CREB3 and Kruppel-like factor 2 can inactivate CXCR4, thereby repressing cell migration [54–55]. The oncogene Her2 can block the ubiquitination process and the degradation of CXCR4 after CXCL12 binds in breast cancer cells [46, 56]. CXCR4 expression is significantly associated with vascular endothelial growth factor (VEGF) production [57] and worse prognosis [58] in cancers. Resveratrol reduces VEGF secretion, via the inhibition of CXCR4 production due to the inactivation of NF-κB [59].

2. CXCR4 /CXCL12 AXIS IN CANCER AND CANCER STEM CELLS

So far, sixteen out of nineteen human chemokine receptors have been detected in cancer cells [60–63]. CXCR4 is frequently over-expressed in malignant cells, including those with the highest incidence, such as cancers of the brain, breast, colorectal, lung, pancreas, prostate, and ovarian, leukemia, and melanomas [10, 64–67]. CXCR4 mediates epithelial cell migration via the activation of Rac1, matrix metalloproteinases MMP-14 and MMP-2 [68], and increases motility of cancer cells through the up-regulation of NF-κB and ERK dependent pathway [69]. The CXCL12/CXCR4 axis regulates angiogenesis [70–72], induces epithelial-mesenchymal transition (EMT) [73–74], and promotes cancer progression and metastasis [75–78]. Prior to the metastatic process, the cancer cells must interact with a variety of stromal cells [79–82]. Therefore, blocking the CXCL12/CXCR4 axis by IL-24 may inhibit cancer cell migration, metastasis and induce apoptosis [83–84]. Chemotaxis of cancer cells, adhesion between cancer and endothelial cells, degradation of extracellular matrix are all necessary steps for cancer cells to survive in circulation, migration and proliferate in targeting organs and tissues [85]. Decreased CXCR4 production by genetic knockdowns of CXCR4 significantly inhibits cancer cells' ability to distant invasion [75].

The chemokine CXCL12 is detected in common sites of tumor metastasis, including lungs, lymph nodes, bone marrow, liver, as well as in animal models, and expressed in circulating cancer cells [12, 86]. CXCR4 stimulates cancer metastasis to organs where its ligand, CXCL12, is produced in large quantity. The interaction between CXCL12 and CXCR4 causes tumor cells to form metastatic tumors [12]. In addition, CXCL12 hypermethylation was reported in number of cancers, such as gastric cancer [87], breast cancer [88–89], colon cancer [90], lung cancer [91], as well as prostate cancer [92] indicating that CXCL12 may have a role in carcinogenesis.

CSCs are a small population of tumor cells that possess the stem cell property and initiate, drive carcinogenesis contributing to tumor cellular heterogeneity [93–95]. Many cancers

possess an enhanced tumor-initiating capacity and generally observed to be more resistant to conventional anticancer therapeutics than other cancer cells [96–99]. There are a number of cellular molecules that may contribute to CSC properties, including Aldehyde dehydrogenase (ALDH) [100–101], Stem cell factor receptor (CD117) [102–103], Pgp-1 (CD44) [104–106], Prominin-1(CD133) [107–108], Urokinase plasminogen activator (CD87) [109], Side population (SP) [110–112], *et al.* There are also a number of pathways, such as Notch [100, 113–114], Hedgehog (Hh) [115–116], Wnt [117–118], JNK [119–120], IL-6/STAT3[121–122], as well as CXCR4 [74] that were identified in the self-renewal of CSC. The increased CXCL12 and CXCR4 mRNAs were recognized in stem cell marker, ALDH positive populations in human H1299 and H460 lung cancer cells and murine LLC [123]. The combined use of Lgr5 and CXCR4 may facilitate the enrichment of CSCs in colorectal cancer, and that treating Lgr5+/CXCR4+ colorectal cancer cells may improve the outcome of colorectal cancer therapy [124]. Recent report also supports that CXCR4 is potentially an ideal target for lung CSC [125]. CD133(+)/CXCR4(+) CSC from patient-derived xenografts (PDX) of non-small cell lung cancer cancer (NSCLC) are associated with initiate metastasis at distant organs and poor clinical outcome [74]. Therefore, CD133/CXCR4 axis may provide novel targets for combinational therapies, as well as prognostic markers in the treatment of NSCLC [126–127].

3. CXCR4 /CXCL12 AXIS AS A THERAPEUTIC TARGET FOR CANCER

As discussed above, the communication between CXCR4 and CXCL12 contributes to the evolution and progression of cancer cells by activating multiple signaling pathways to enhance tumor cell invasion and distant metastasis [61, 128–130]. CXCR4 also regulates tumor vascularization and EMT, further strengthening the interaction between tumor cells and stromal cells [131]. CXCR4 cooperates with other transcriptional factors, such as NF-κB, Nanog, and Bmi-1 and contributes to the maintenance of stemness and induction of metastasis behavior in CSC [132–135]. It is proposed that therapies for cancer patients that specifically target CSC signaling pathways could be valuable in combating this disease [96, 136–138]. Without question, the CXCL12/CXCR4 axis is believed to be a novel drug target for cancer therapy. A schematic depiction of the effects of CXCL12/CXCR4 in cancer are shown in Fig. (1).

In the past ten years, a number of inhibitors of CXCL12/CXCR4 which are able to attenuate the growth of tumor cells *in vivo* and *in vitro* have been reported We summarize the effects of various CXCR4 inhibitors on tumor in Table 1. So far, CXCR4 antagonists are developed by a number of programs, including five major classes: (1) small modified peptides, including BKT140 [139], FC131 [140–141], T140 [142], POL6326 [143], TF14016 [144]; (2) small-molecules, including the bicyclam AMD070 [145–146], AMD3100 [130, 147–149], AMD11070 [150], MSX-122 [151], GSK812397 [152–153], KRH-3955 [154–155]; (3) antibodies, such as MDX-1338/BMS 93656 [156]; (4) modified agonists and antagonists for CXCL12 such as CTCE-9908 [157–158] ; (5) microRNAs, such as miR-302a [159], miR-9 [160], miR-204-5p[161] and miR-126 [162].

T140 analogs were previously developed as anti-HIV agents [142]. Liang et al further increased the potency of T140 to generate a synthetic antagonist 14-mer peptide compound,

TN14003 (BKT140) [163]. A strong CXCR4 inhibitor, TN14003 is as an adjuvant treatment for traditional anticancer therapies against human NSCLC [132, 164]. Using TN14003 as a template, a first nitrogen atom substitution of the terminal aromatic rings was named as WZ811[165], while a second nitrogen atom substitution was named as MSX-122. Both MSX-122 and WZ811 inhibit lung metastasis of breast cancer.

AMD3100, also known as plerixafor, is able to inhibit the binding of CXCL12 to CXCR4[166]. AMD3100 inhibited CXCR4 internalization and chemotaxis of acute lymphoblastic leukemia (ALL) cells. AMD3100 was demonstrated to prevent relapse of extramedullary ALL cells after chemotherapy [167]. A phase I/II study of 52 patients with relapsed or refractory acute myelogenous leukemia (AML) using AMD3100 showed encouraging rates of remission with correlative *in vivo* evidence of the CXCR4/CXCL12 axis disruption [168]. These encouraging data led to randomized phase III clinical trials of AMD3100 in patients with relapsed AML. AMD3100 is currently tested in the treatment of solid tumors. AMD3100 was demonstrated to reduce the growth of the primary small cell lung cancer by 61% ($P<0.05$) and additionally suppress metastasis formation by 43% [169]. AMD3100 was also reported to efficiently impair tumor growth and metastasis dissemination in both Herceptin-sensitive and Herceptin-resistant HER2 breast cancer [170].A phase I/II study of AMD3100 in breast cancer patients indicated preliminary signs of efficacy [171].

Antibodies have also been used to disrupt the CXCR4 pathway. BMS-936564/MDX-1338, a fully human IgG(4) monoclonal antibody can specifically recognize human CXCR4 [156]. MDX-1338 has shown antitumor effects in established tumors, such as AML, NHL, and multiple myeloma xenograft models [156].

CTCE-9908 is a modified peptide antagonist for CXCL12 corresponding to the N-terminal region of CXCL12 chemokine. It was reported to decrease expression levels of VEGF and slow the rate of primary tumor growth. CTCE-9908 administration in combination with docetaxel reduced tumor volume than that with docetaxel alone. CTCE-9908, in combination with DC101, an anti-angiogenic agent, also reduced primary tumor volume and distant metastasis than DC101 alone [172].

MicroRNAs have been reported to play critical roles in regulating tumor progression through CXCL12/ CXCR4 axis [159]. MiR-302a decreased the invasion and metastasis of breast cancer cells by reducing CXCR4 production [173]. MiR-9 reduced the proliferation of oral squamous cell carcinoma cells by the inhibition of CXCR4 via the Wnt/β-catenin signaling pathway [160]. MiR-146a downmodulated CXCR4 production in target cells [174]. CXCR4 was inhibited upon miR-451 treatment in lung cancer cells [175]. MiR-204-5p may function as an inhibitory RNA molecule in oral squamous cell carcinoma by targeting CXCR4 [161]. Artificial microRNA was demonstrated to effectively block invasion and metastasis of breast cancer cells by targeting CXCR4 [176]. MiR-126 may also act as a tumor suppressor by inactivating RhoA signaling via CXCR4 in colon cancer [162].In addition, miR-101 was recently discovered to directly target CXCL12 in lung cancer cells [177].

4. TARGETING CXCL12/CXCR4 AXIS AND IMMUNOTHERAPY

Tumor immunotherapy has entered a phase of rapid development, based on the notion that the immune system is the best tool humans have for fighting disease, and that the immune system is capable of recognizing tumors and eliminating malignant cells. Treatment with anti-PD ligand-1 (anti–PD-L1) [178–180], anti-programmed death-receptor 1 (anti–PD-1) [181–182], checkpoint antagonists including anti-cytotoxic T lymphocyte antigen-4 (anti–CTLA-4) [183–184], as well as engineered CAR T cells [185–187], has induced striking responses in subsets of patients with a range of solid tumors. With the FDA approval of the two anti–PD-1 antibodies, pembrolizumab (formerly MK-3475 or lambrolizumab; Merck) and nivolumab (Bristol-Myers Squibb), sipuleucel-T, ipilimumab (anti–CTLA-4; Bristol-Myers Squibb), immunotherapy has become a mainstream treatment option for some cancers [188–190]. Despite the unprecedented rates of durable clinical responses observed in patients affected by advanced solid tumors[181, 191–192], many more patients with solid tumors resistant to immunotherapy such as ovary, colon, and pancreatic cancer have not yet benefited from immunotherapeutic approaches, and the mechanism of the resistance may be related to the CXCL12/CXCR4 axis. The carcinoma-associated fibroblasts (CAF) in solid tumors was were reported to have an immunologic inhibition function in recent studies. Immune suppression by the fibroblast activation protein-α (FAP) positive CAF is regulated by CXCL12 binding to cancer cells and excluding T cells, which relies on the signaling of CXCR4. The conditional depletion of the FAP^+ CAF permits immune control effects of both anti–PD-L1and anti–CTLA-4; administering AMD3100, induced rapid T-cell accumulation in this autochthonous model of pancreatic ductal adenocarcinoma (PDA), and anti-PD-L1 to synergistically diminish cancer cells. The residual tumor was only composed of inflammatory cells and premalignant epithelial cells [193–194]. These results indicate that the fibroblastic component of tumors may be critical in the adaptation of cancer to the host. Another study [195] demonstrated that the up-regulation of CXCL12 alpha in HCC models increased hypoxia, increased the recruitment of immunosuppressive cells, indicated intratumoral expression of the immune checkpoint inhibitor PD-L1, and accumulated of T-regulatory cells and M2-type macrophages after treatment of sorafenib. PD-1 blockade combined with CXCR4 inhibition and sorafenib decreased HCC growth [195]. In this study, AMD3100 inhibited the polarization toward an immunosuppressive microenvironment, reduced tumor growth, decreased lung metastasis, and improved animal survival. Thus, anti-PD-1 had additional antitumor activity upon combined with sorafenib and AMD3100 in HCC models.

CONCLUSION AND OVERALL PERSPECTIVES

Over the past ten years, despite advances in techniques and protocol of diagnosis and therapies, cancer mortality remains high. Better understanding of the disease and more efficacious treatments for cancer patients are clearly needed. CXCL12 is a member of chemokines expressed by a variety of cells in bone marrow, liver, lungs, lymph nodes, stromal cells (fibroblasts) and endothelial cells. Binding of CXCL12 to its specific G protein-coupled receptor CXCR4 induces a plethora of downstream signaling events involving ERK1/2, ras, PLC/ MAPK, p38 MAPK, and SAPK/ JNK, which in turn are responsible for various biological and pathological processes including the regulation of

hematopoiesis and apoptosis, immunity and mitogenic activity, cancer cell growth, migration, dissemination, and neovascularization. Aberrant CXCR4 production was significantly higher in many tumor tissues. Thus, the CXCL12/CXCR4 axis has emerged as a novel target for cancer therapeutics. CXCL12/CXCR4 antagonists have been developed and validated, which have shown promising anti-cancer activities in several tumor cell types. Five major classes of CXCR4 antagonists have been identified: (1) small modified peptides; (2) small-molecules; (3) antibodies to CXCR4; (4) modified agonists and antagonists for CXCL12; (5) microRNAs. The mechanism underlying tumor resistance to immunotherapy may relate to the CXCL12/ CXCR4 axis. Therefore, the CXCL12/CXCR4 axis cannot only be a target for monotherapy, but also be used synergistically with immunotherapy for cancer patients.

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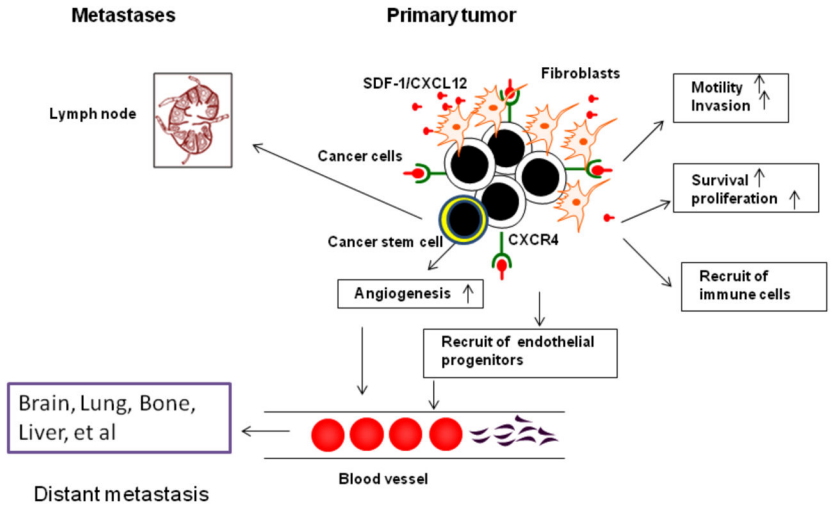

Fig. 1. Potential Roles for CXCL12/CXCR4 in Cancer and Cancer Stem Cells

Cancer cells and cancer stem cells express CXCR4, and both cancer cells and fibroblasts produce SDF-1(CXCL12). Tumor cells expressing CXCR4 directs metastasis to sites such as liver, bone, pericardium,adrenal glands, spinal cord and brain. SDF-1/CXCR4 functions locally in autocrine and paracrine ways to increase tumor growth in primary locations. Tumor and tumor microenvironment secreted SDF-1 promote tumor cell survival, growth and also the recruitment of bone marrow derived cells and immune cells into the tumor environment.

Table 1

The effects of various CXCR4 inhibitors on tumor.

Compound	Type of Studies	Biological Function on Cancer	References
T140	*In vitro, in vivo*	Inhibition of SDF-1 induced cancer cell migration	[142, 196]
TN14003	*In vivo*	Limiting metastases of breast cancer, a radiotracer to detect CXCR4- positive cells; inhibiting leukemia and multiple myeloma tumor growth	[163, 170, 197]
AMD3100	*In vivo*	Reduce lung metastases of breast cancer; sensitizing prostate cancer to docetaxel chemotherapy	[198–200]
GST-NT21MP	*In vivo*	Decrease in SDF-1-induced cell growth, adhesion, migration	[201]
CTCE-9908	*In vivo*	Anti-tumor growth and anti-metastatic effects	[158, 202–204]
ALX40-4C	*In vitro*	Prevent breast cancer spread	[205]
Baohuoside	*In vitro, in vivo*	Antiproliferative and antimetastatic effect on cancer through the downregulation of CXCR4 expression	[206–207]
Ginsenoside Rg3	*In vitro*	Reduce CXCR4 expression and migration and invasion	[208]
AKBA	*In vitro, in vivo*	Abolish tumor cell invasion and metastasis	[209–210]
Butein	*In vitro,*	Reduce SDF-1-induced migration and invasion of breast cancer	[211]
WZ811	*In vitro, in vivo*	Inhibition of Matrigel invasion; suppression of chronic lymphocytic leukemia progression	[165, 212]
MSX-122	*In vitro, in vivo*	Inhibition of cAMP and Matrigel invasion	[151]
AMD3465	*In vitro, in vivo*	Reduction of cancer growth and metastasis	[213–214]
4EGI-1	*In vitro*	Selectively inhibits translation of mRNAs of CXCR4, targeting cancer stem cell	[215]
508MCl	*In vivo*	Interfering with CXCR4 function with high potency and specificity	[216]
Celastrol	*In vitro*	Downregulation of CXCR4 expression	[217]
Thymoquinone	*In vitro*	Downregulation of CXCR4 expression	[218]
Benzenesulfonamides	*In vitro*	Inhibition of CXCR4	[219]