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CXCL12/CXCR4/CXCR7 Chemokine Axis and Cancer Progression

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Abstract

Chemokines, small pro-inflammatory chemoattractant cytokines that bind to specific G-protein coupled seven-span transmembrane receptors (GPCRs), are major regulators of cell trafficking and adhesion. The chemokine CXCL12 [also called stromal-derived factor-1 (SDF-1)] is an important α-chemokine that binds primarily to its cognate receptor CXCR4 and thus regulates the trafficking of normal and malignant cells. For many years it was believed that CXCR4 was the only receptor for CXCL12. Yet recent work has demonstrated that CXCL12 also binds to another seven-transmembrane span receptor called CXCR7. Our group and others have established critical roles for CXCR4 and CXCR7 on mediating tumor metastasis in several types of cancers, in addition to their contributions as biomarkers of tumor behavior as well as potential therapeutic targets. Here we review the current concepts regarding the role of CXCL12/CXCR4/CXCR7 axis activation, which regulates the pattern of tumor growth and metastatic spread to organs expressing high levels of CXCL12 to develop secondary tumors. We also summarize recent therapeutic approaches to target these receptors and/or their ligands.

1. Introduction

Chemokines are a superfamily of chemoattracting, cytokine-like proteins that bind to and activate a family of chemokine receptors. Over 50 chemokines have been identified, and they are divided into 4 families (CXC, CX3C, CC, and C) on the basis of the positions of 4 conserved cysteine residues [1].

Chemokine receptors are seven-transmemberane receptors coupled to G-proteins, all with their N-terminus outside the cell surface, three extracellular and three intracellular loops as well as a C-terminus in the cytoplasm. One of the intracellular loops of the chemokine receptors couples with heterotrimeric G-proteins, and that mediate ligand binding to the receptor which initiates a cascade of signal transduction events [2].

Most chemokine receptors are promiscuous as each can bind with high affinity to multiple chemokine ligands (CXCR, CCR, XCR, and CX3CR). As a result there is a high degree of

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redundancy in the chemokine family as multiple chemokines bind to the same receptor [3]. This feature may represent an essential feature for fine tuning of specific responses. In general, the CC receptors are more promiscuous than the CXC receptors [4]. Some chemokines bind to multiple receptors and some receptors in turn bind multiple chemokines, whereas certain chemokines interact with single receptor and some receptors bind only one chemokine. (Fig. 1).

To date, at least 20 chemokine receptors (CCR1-11, CXCR1-7, XCR1, and CX3CR1) have been identified. Chemokines and their receptors are now known to play important roles in inflammation, infection, tissue injury, allergy, cardiovascular diseases, and malignant tumors [5].

One of the most intriguing and perhaps important roles that chemokines and the chemokine receptors have is in regulating metastasis. Here, chemokine receptors may potentially facilitate tumor dissemination at each of the key steps of metastasis, including adherence of tumor cells to endothelium, extravasation from blood vessels, metastatic colonization, angiogenesis, proliferation, and protection from the host response via activation of key survival pathways such as ERK/MAPK, PI-3K/Akt/mTOR, or Jak/STAT, et al [6–8]. In addition, it is increasingly recognized that chemokines play an important role in facilitating communication between cancer cells and non-neoplatic cells in the tumor microenvironment(TME), including endothelial cells and fibroblasts, promoting the infiltration, activation of neutrophils and tumor-associated macrophages (TAMs) within the TME [9,10]. In this review, we mainly focus on the roles of chemokines CXCL12 and its cognate receptors CXCR4 and CXCR7 as they pertain to cancer progression.

2. CXCL12, CXCR4 and CXCR7

2.1 CXCL12/SDF-1

Stromal-derived factor-1 (SDF-1 or CXCL12) is a CXC chemokine. It was first cloned from a bone marrow-derived stromal cell line and was later identified as a pre-B-cell growth stimulating factor (PBSF). CXCL12 is broadly expressed in a variety of tissue types where it acts as a potent chemoattractant for immature and mature hematopoietic cells [11,12]. CXCL12 has been identified as playing an important role in the homing of hematopoietic stem cells to the bone marrow and mediate the survival as well as the proliferation of human and murine progenitor cells [13–15]. CXCL12 has two major isoforms, α and β [16]. Both are derived from a single gene, while CXCL12β differs by an additional four amino acids (RLKM) at the C-terminal end due to alternative splicing [17]. CXCL12α is the predominant isoform secreted by marrow stromal cells and endothelial cells and is found in nearly all organs. The α-isoform secretion enhances tissue damage but undergoes rapid proteolysis in blood [18]. In contrast, the β-isoform is more resistant to blood-dependent degradation, stimulates angiogenesis and is present in highly vascularized organs such as liver, spleen, and kidneys [18]. The secretion of CXCL12 within or around injured tissues is a crucial event that may create a microenvironment which faciliates the homing of circulating endothelial tissue-committed stem cells (TCSCs) and the affected tissue resulting in organ regeneration or tissue repair [19].

Four additional human isoforms of CXCL12 have been reported, all with chemotactic activities [20]. They are derived from alternative splicing events sharing the same first three exons, but use different fourth exons, described as CXCL12γ (gamma), CXCL12δ (delta), CXCL12ε (epsilon) and CXCL12φ (phi) [20]. CXCL12γ is located in very active, less vascularized organs susceptible to infarction such as the heart and the brain [18]. CXCL12δ is predicted to be more than 50% longer than CXCL12α [20]. Whether the additional amino acids affect affinity or activity of this ligand for its receptor remains unclear.

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In bone marrow, CXCL12, is mainly produced by osteoblasts lining the bone endosteum [21–23], and regulates the migration of $CD34^+$ cells, where the chemoattractant activity is significantly inhibited by pretreatment of $CD34^+$ cells with either neutralizing anti-CXCR4 antibodies or neutralizing CXCR4 peptides [22], suggesting the existence of CXCL12/CXCR4 functional binding on $CD34^+$ cells. CXCL12 preferentially induced the migration of repopulating cells of SCID mice [24]. Consistently, human $CD34^+$ cells are capable of repopulating the marrow of NOD/SCID mice with multilineage hematopoiesis [25]. Interestingly, DNA-damaging agents such as irradiation, cyclophosphamide, or 5-fluorouracil increase CXCL12 expression in both mouse marrow and in cultured cells [25,26]. The CXCL12 promoter contains two HIF-1α binding sites, and CXCL12 expression is enhanced in endothelial cells expressing HIF-1α [27]. Elevation of HIF-1α expression in either hypoxic or damaged tissues results in the elevation of CXCL12 levels which results in the chemoattraction of $CXCR4^+$ tissue-committed stem cells (TCSCs) that participate in tissue regeneration [27].

2.2 CXCL12 receptors

2.2.1 CXCR4—CXCR4 is a highly conserved seven-span transmembrane GPCR that binds the ligand CXCL12α. CXCR4 has received considerable attention since it serves as a co-receptor for entry of T-tropic (X4) HIV viruses that target $CD4^+$ T cells [28,29]. During development, CXCR4 is expressed in a broad range of tissues, including immune and the central nervous systems and can mediate migration of resting leukocytes and hematopoietic progenitors in response to CXCL12 functioning in a number of physiological processes [30–33]. In the immune system, CXCR4 is highly expressed by monocytes, B cells, and naïve T cells in peripheral blood as well as early hematopoietic progenitor cells in bone marrow [34]. Differential expression of CXCR4 in $CD34^+$ progenitor cells may be involved in maintaining hematopoietic progenitor cells in the marrow and regulating stem cell trafficking [35]. Studies have demonstrated that CXCL12 / CXCR4 axis plays an important role in development. For example, the deficiency of this axis leads to circulatory, CNS, immune, and hematopoietic defects [36,37].

Once CXCL12 binds to CXCR4, the receptor forms a complex with the Gαi subunit G protein, resulting in inhibition of adenylyl cyclase–mediated cyclic adenosine monophosphate (cAMP) production and mobilization of intracellular calcium. Dissociation of the Gαi subunit from Gβγ leads to activation of multiple downstream targets, including ERK1/2, MAPK, JNK, and AKT effectors [38–41]. Ligand-stimulated chemotaxis is accompanied by cytoskeletal rearrangements, actin polymerization, polarization, pseudopodia formation, and integrin-dependent adhesion to endothelial cells and other biologic substrates.

To date, CXCR4 is one of the most common chemokine receptor that has been demonstrated to be over expressed in more over 23 human cancers, including breast cancer, ovarian cancer, melanoma, and prostate cancer (PCa) (as reviewed in [42]), Although CXCR4 is expressed in a broad array of tissues, CXCR4 expression is low or absent in many normal tissues, including breast [43] and ovary [44].

CXCR4 expression is up-regulated in malignant cells via several mechanisms. VEGF is a known inducer of CXCR4 expression, and it has been shown that HIF-1 acts upstream to induce VEGF [45]. HIF-1 is a heterodimeric transcription factor responsive to oxygen concentrations in tissues and has been shown to up-regulate CXCR4 expression. Thus, in hypoxic regions of expanding tumors, chemokine receptor levels might be increased to facilitate survival and escape from the primary tumor mass. In addition to facilitating distant metastasis, HIF-1 has been shown to induce CXCR4 in gliomas, leading to enhanced proliferation, resistance to apoptosis, and local invasion [45].

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2.2.2 CXCR7/RDC-1—The concept of an exclusive interaction of CXCL12 with CXCR4 was challenged after it was noticed that murine fetal liver cells from CXCR4 knockout mice still may bind CXCL12 [46]. In addition, discrepancies were observed between CXCR4 expression and CXCL12 binding affinity in several human cancer cell lines [46]. These observations suggest a presence of another CXCL12 binding receptor. This receptor was recently identified and named CXCR7 (or RDC-1) [46,47], which was originally cloned on the basis of its homology with conserved domains of GPCRs [48]. The CXCR7/RDC-1 gene maps to mouse chromosome 1 and human chromosome 2, where the genes encoding CXCR1, CXCR2, and CXCR4 are located. CXCR7/RDC-1 shares homology with the viral gene ORF74 encoding a chemokine receptor that suggests that it may signal constitutively in the absence of ligand. In addition to CXCL12, CXCR7 binds with low affinity to the chemokine CXCL11 (I-TAC) [46]. CXCR7 expression has been found in T lymphocytes and during CXCL12-mediated chemotaxis [47]. CXCR7 expression is tightly regulated in B cell development and differentiation. The expression of CXCR7 correlates with the ability of B cells to differentiate into plasma cells upon activation, suggesting that CXCR7 is a marker for memory B cells, which are competent to become antibody secreting cells [49,50].

CXCR7 expression has been shown to be elevated in endothelial cells associated with tumors [51]. Membrane-associated CXCR7 is expressed on many tumor cell lines, on activated endothelial cells, and on fetal liver cells [46]. CXCR7 is expressed by the placenta [52] as well as in the vascular endothelium [53,54]. These characteristics suggest that like CXCR4, CXCR7 plays a role in regulating immunity, angiogenesis, stem cell trafficking, and mediating organ-specific metastases of cancer..

However, growing evidence has suggested that CXCR7 functions as a decoy receptor, which does not activate Gi pathways of a chemokine receptor that would result in GTP hydrolysis or calcium mobilization [46]. Yet CXCR7 significantly increases cell proliferation and elevates cellular adhesion property in other conditions [46,50,53,55]. Thus debate has arisen whether CXCR7 functions like GPCR mediating the signal transduction process [56]. As a result, several mechanisms underlying CXCR7 function have been proposed. One role that CXCR7 may play is to scavenge or sequester CXCL12α, thereby generating gradients of CXCL12α that lead to differential signaling by CXCR4 [57,58]. Another role for the receptor is that it may serve as a co-receptor for CXCR4 [59,60] and enhances CXCL12-mediate G protein signaling [59], as the two receptors form heterodimers in the context of overexpression in transiently transfected cells. These observations suggest that ligand binding to CXCR7 results in crosstalk with CXCR4 mediated by intracellular signaling molecules [61]. More recently, it has been demonstrated that CXCR7 interacts with β-arrestin in a ligand dependent manner [56,62,63]. CXCR7 can signal through β-arrestin and act as an endogenous β-arrestin-biased receptor, which suggests that other receptors that are currently thought to be orphans or decoys may also signal through non-G protein-mediated mechanisms [56].

2.3 CXCL12 and CXCR4/CXCR7 axis in cancers

2.3.1 Prostate cancer (PCa)—The binding of CXCL12 to CXCR4 initiates divergent signaling pathways downstream of ligand binding, which can lead to multiple responses. One mechanism as to how PCa utilizes the CXCR4 receptor is whether CXCL12 act as a growth factor? Kukreja et al. reported that CXCL12 treatment of PC3 human PCa cells lead to MEK, IKK and IκBα phosphorylation [64]. This leads to nuclear localization of NF-κB followed by transcription and expression of CXCR4. These data suggest that CXCL12α-induced expression of CXCR4 in PC3 cells is dependent on MEK/ERK signaling cascade and NF-κB activation which is critical for tumor cell survival. Further works are needed to explore the network of signaling pathways triggered by CXCL12/CXCR4 axis.

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Previous works by our group and others have found that CXCL12/CXCR4 axis plays a central role in PCa progression. Sun et al. showed that the levels of CXCL12 in human and mouse tissues were higher in the preferable sites of metastasis for PCa cells (i.e. bone, liver, and kidney), compared with tissues rarely affected (i.e. lung, tongue, and eye) [65]. CXCL12 was localized to the metaphysis of the long bones, nearest the growth plate, but not in the center of bone marrow [65]. In addition, CXCL12 increased the adhesion of PCa cells to an endothelial cell monolayer and to immobilized fibronectin, laminin, and collagen [66,67], and to osteosarcoma cells [23]. This might occur through an up-regulation of α5 and β3 integrins [66]. In an *in vivo* metastasis model, neutralizing antibody against CXCR4 limited the extent of bone metastases and the antibody and blocking peptide of CXCR4 limited the growth of intraosseous prostate cancer cells after intratibial injections [65]. These data provided evidence that CXCL12/CXCR4 participates in localizing tumors to the bone marrow in PCa [23,65,68].

Darash-Yahana et al., demonstrated that PCa tumor-associated blood vessels and basal cell hyperplasia expressed CXCL12 [69]. Subcutaneous xenografts of PC3 cells that over expressed CXCR4 in a mouse model were demonstrated significantly greater blood vessel density, functionality, invasiveness of tumors into the surrounding tissues. Neutralizing the interactions of CXCL12/CXCR4 with antibodies against CXCR4 inhibited the CXCR4-dependent tumor growth and vascularization [69]. Moreover, CXCL12 was report to trigger an angiogenic switch, through the up-regulation of vascular endothelial growth factor (VEGF) and CXCL8, as demonstrated using CXCR4 siRNA [70]. Interestingly, CXCL12 down-regulated the glycolytic enzyme phosphoglycerate kinase 1, which was a negative regulator of VEGF and CXCL8 expression [71].

In the tumor microenvironment, cultured prostate cancer-associated fibroblasts (CAFs) expressing high levels of CD90 (hi) were isolated and analyzed for a tumor-promoting phenotype. Co-culture or conditioned medium from CD90(hi) cells increased CXCR4 expression in BPH-1 epithelial cells, at least in part due to TGF-beta, and protected BPH-1 cells from apoptosis [72]. These data suggest that CAFs may get involved in tumor progression.

Although expression of CXCR4 was found on almost all types of tissue-committed stem cells in the body [73], CXCR4 identified on PCa stem cells remains uncertain. One group reported that in the invasive front of pancreatic tumors, a distinct subpopulation of $CD133^+$ $CXCR4^+$ cancer stem cells was identified that determines the metastatic phenotype of the individual tumor [74]. Similarly, the role of $CD133^+$ $CXCR4^+$ and/or $CXCR7^+$ PCa stem cells is not yet known. So far, functional CXCR7 was only identified on renal progenitor cells [75].

We recently reported that CXCR7 is highly expressed on human PCa cells [54]. Staining of high-density tissue microarrays demonstrated that CXCR7 expression at the protein level was greater on aggressive tumors. Furthermore, studies on established PCa cell lines revealed that CXCR7 regulated cell proliferation most likely because of the enhanced cell survival, adhesion, and chemotaxis. In addition, CXCR7 increased expression of proangiopoietic factors such as IL-8 and VEGF [54]. Interestingly, the CXCR7 levels are influenced by CXCR4 activation. Evidence was also found that CXCR7 signaling in PCa cell lines results in phosphorylation of serine/threonine kinase Akt. PCa cells over-expressing CXCR7 grew faster with a higher density of neovessels in an immunodeficient mouse model [54]. Indeed, because hypoxia induces CXCR7 by endothelial cells, and is expressed by tumor-associated vessels, the contribution of CXCR7 in neoangiogenesis and formation of tumor vasculature is likely. It is not clear however at this point how important

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the interaction between CXCL12 and CXCR7 is in chemoattraction of endothelial progenitors.

Furthermore, our group recently found that hypermethylated in cancer (HIC1), a suppressor gene, is a potential upstream target of CXCR7, which is generally silenced by hypermethylated in CpG islands in PCa. Luciferase promoter assays revealed that a functional conserved HiRE (HIC-responsive element) in PCa cells inversely regulated CXCR7 expression (unpublished data). These observations raise a possibility that alteration of HIC1 expression by epigenetic approach may inhibit CXCR7 level in cancer cells, which provide an optional proposal in cancer treatment.

2.3.2. Breast cancer—Muller et al. reported in breast cancer that CXCR4 and CXCL12 are central players in regulating metastasis by showing that normal breast tissues express little CXCR4, whereas breast neoplasms express high levels of CXCR4 [43]. CXCR4 signaling in response to CXCL12 mediates actin polymerization and pseudopodia formation, and subsequently induces chemotactic and invasive responses [43]. These data formed the basis of the hypothesis that malignant cells may employ chemokine receptors to migrate toward chemokine ligands expressed at common metastatic sites, such as the lungs, bone marrow, and lymph nodes. Indeed, CXCR4 appears to be one of a limited number of genes that are enriched in a subpopulation of metastatic breast cancer cells, as over expression of CXCR4 alone significantly increased numbers of bone metastases *in vivo* [76]. Supporting evidence for the hypothesis was demonstrated by Liang et al., as blocking CXCR4 expression by siRNAs decreased breast cancer cell invasion in an *in vitro* assay and inhibited metastasis in an animal model [77]. Interestingly, the CXCR4 carboxy-terminal domain (CTD) appears to play a major role in regulating receptor desensitization and down-regulation [78]. Whereas deletion of the C-terminal domain of CXCR4 leads to the down-regulation of cell-to-cell contact, enhanced motility and proliferation in breast carcinoma cells [78].

Elucidation of the underlying mechanisms of breast cancer invasion and metastasis focused on CXCR4 has resulted in several important observations. Ligand-binding studies indicate that the number and affinity of CXCR4 receptors are similar in nonmetastatic cells versus highly metastatic cells. In metastatic cells, CXCL12 binding to the Gαβγ/GDP protein complex leads to a GTP-for-GDP exchange, allowing Gαi to dissociate from the Gβγ subunit, leading to activation of ERK1/2, IκBα, JNK, Akt, p38 MAPK, and GSK-3αβ. In nonmetastatic cells, CXCR4 is able to independently form a complex with Gαi or Gβ subunits, but no Gαβγ heterotrimer could be associated with CXCR4 and, ultimately, Gβγ-dependent downstream signaling did not occur [79]. Although the molecular basis for the difference in G protein signaling in metastatic versus nonmetastatic cells remains to be elucidated, these studies have implications for clinical studies that are examining CXCR4 protein expression but not receptor function. As observed in breast cancer cell lines, detection of CXCR4 protein does not necessarily indicate CXCR4-mediated signaling [80].

There is increasing evidence that CXCR4 interacts with several growth factor receptor tyrosine kinases. Upon activating IGF-1R, IGF-1 was shown to transactivate CXCR4 signal transduction in metastatic MDA-MB-231 cells but not to activate nonmetastatic MCF-7 cells, even though both cell lines are positive for IGF-1R and CXCR4 [81]. Myofibroblasts associated with breast cancer, but not those in normal breast tissue, produce CXCL12 and enhance growth of tumors through mechanisms that include proliferation and survival of malignant cells and angiogenesis [9,82]. Specific alleles of CXCL12 are associated with an increases risk of breast cancer [83], and CXCL12 has been shown to transactivate Her2/neu, an established oncogene in breast cancer [84].

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A role of CXCR7 in cell growth/survival was first indicated by an observation that CXCR7-transfected MDA-MB-435s cells expanded more rapidly in culture than the control cells [46]. Expression of CXCR7 confers a survival advantage to cells that becomes experimentally evident using tissue culture conditions that are suboptimal for cell growth [46]. In the same study, CXCR7 transfectant cells adhered to the activated human umbilical vein endothelial cell (HUVECs) markedly more than did the wild-type cells and even showed some adherence to unstimulated HUVECs [46]. Further data revealed that the HUVECs up-regulate CXCR7 expression after *in vitro* stimulation with TNF-α and IL-1β. Increased CXCR7 mRNA expression was also observed after HUVEC activation. Similar results were obtained using endothelial cells derived from lung, heart, and various other tissues [46]. Likewise, MDA-MB-435s CXCR7-transfected cells formed larger tumors than wild type or MDA-MB-435s vector-transfected control cells [53], In the mouse 4T1 cells animal model, CXCR7 expression dramatically enhances growth of cell-derived breast tumors [53]. Moreover, expression of CXCR7 on breast cancer cells enhances ability of these cells to seed and proliferate in lung metastases [53]. Another study has shown that high levels of CXCR7 in breast cancer facilitates cancer cells ability pass through the hemato-encephalic barrier, which lead to brain metastasis [85].

2.3.3 Lung cancer—Small cell lung cancer (SCLC) is an aggressive and rapidly metastasizing neoplasm with a high propensity for marrow involvement. Burger et al. reported that SCLC cells expressed high levels of functional CXCR4 receptors, and demonstrated CXCR4 activation induced migratory and invasive responses and adhesion to marrow stromal cells in a CXCR4- and integrin-dependent fashion [86,87]. CXCL12/CXCR4 axis is the important mediators for the adherence of SCLC cells to ECM proteins like fibronectin, collagen I and VCAM-1 [88]. CXCR4-induced adhesion of SCLC cells to marrow stromal cells protects against etoposide-induced apoptosis [88]. The CXCR4 antagonist T140 and its derivates blocks the CXCR4-mediated adhesion to ECM components and thereby altered SCLC chemosensitivity [88]. Collectively, these studies indicate that expression of CXCR4 by SCLC cells facilitates the activation of integrins that regulate the adhesion of tumor cells to the marrow microenvironment, which in turn confers drug resistance and facilitates tumor cell growth. Moreover, CXCR4 may direct the distinct metastatic pattern observed in patients with SCLC [9].

Neoplastic cells in non-small cell lung cancer (NSCLC) may also express CXCR4. Interestingly, Su et al. found that differential expression of CXCR4 correlated with metastatic potential *in vitro* and *in vivo*, which suggests that the movement of NSCLC from primary sites to metastatic nodes may be dependent on the levels of CXCR4 [89]. As seen in other tumors, hypoxia is able to induce a significant increase in the expression levels of CXCR4 on NSCLC cells through the VHL-HIF-1α pathway, supporting the notion that HIF-1α-mediated upregulation of CXCR4 may be a common response of tumor cells to hypoxia [90,91].

CXCR7 immunostaining in lung cancer has been shown in samples obtained from multiple patients with squamous cell carcinomas but also its expression can be seen occasionally in lung adenocarcinomas [53]. In vascular endothelium, CXCR7 has been identified on a large percentage of tumor vasculature from human malignancies [53]. CXCR7 is also detected on the surface of murine breast Lewis lung carcinoma (LLC) cell lines and RNAi targeting CXCR7 results in smaller tumor formation than control transfected cells [53]. Similarly, the use of a CXCR7 antagonist, CCX754, develops markedly smaller tumors in mice than those found in animals receiving vehicle only [46]. These data demonstrated the CXCR7 has pro-tumor properties in lung cancer. Recently studies have shown that higher expression of CXCR7 is related to early and metastatic recurrence in pathological stage I NSCLC [92]. In

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keeping with these observations in patients with higher levels of CXCR7 expression, the EGFR mutations are frequently observed [92].

2.3.4 Pancreatic adenocarcinoma—Pancreatic cancer is currently the fourth leading cause for cancer-related mortality. The CXCL12/CXCR4 axis also has an important role in the pancreatic cancer progression through tumor cell migration and angiogenesis [93–96]. Based on the phenomena that undetectable CXCL12 expression was found in all examined pancreatic cancer cell lines, but was identified in all pancreatic cancer tissue samples [95,96], Gao et al. hypothesized that CXCL12/CXCR4 axis functions through paracrine mechanism [97]. The $CXCR4^{+}$ pancreatic stellate cells (PSCs)-conditioned media promoted the proliferation, migration and invasion of pancreatic cancer cells while CXCR4 antagonist AMD3100 significantly inhibited these promotive effects [97]. The relationship between CXCR7 and pancreatic carcinoma not been extensively explored yet one study suggests that patients with $CXCR4^{low}/CXCR7^{low}$ tumor had a significantly shorter 5-year disease-free survival (DFS) and overall survival (OS) than patients with a $CXCR7^{high}/CXCR4^{high}$ tumor [98].

As mentioned above, the expression of CXCR4 is found in almost all types of tissue-committed stem cells in the body. Indeed, in human pancreatic cancer tissue contains cancer stem cells defined by CD133 expression that are exclusively tumorigenic and highly resistant to standard chemotherapy. In the invasive front of pancreatic tumors, a distinct subpopulation of $CD133^{+}$ $CXCR4^{+}$ cancer stem cells had been identified that determines the metastatic phenotype of the individual tumor. Depletion of the cancer stem cell pool for these migrating cancer stem cells significantly reduces the metastatic phenotype of pancreatic tumors without affecting their tumorigenic potential, which indicates that a subpopulation of migrating $CD133^{+}$ $CXCR4^{+}$ cancer stem cells is essential for tumor metastasis [74]. These intriguing findings may suggest the potential therapeutic target for this aggressive disease.

2.3.5 Other malignancies—CXCR4 activation by CXCL12 induces migration and/or survival of neuronal and glial tumors, neuroblastoma cells, colorectal cancer, head and neck, brain, bladder, esophagealcancer, melanoma, renal cell cancer, ovarian cancer, and rhabdomyosarcoma (RMS) [99]. In ovarian cancer, CXCR4 is a dominant chemokine receptor in cancer tissues [100]. CXCL12 has a direct effect on the proliferation of ovarian tumor cells, which are stimulated to grow *in vitro* in the presence of CXCL12 and this pro-proliferative effect can be blocked with neutralizing antibody against CXCR4 or with inhibitor of CXCR4 [101,102].

Zhou et al. demonstrated that over expression of CXCR4 in glioblastoma cell lines enhanced their growth in soft agar, and expression of anti-sense CXCR4 reduces neurite outgrowth and cellular differentiation [103]. Treatment of the glioblastoma cell lines with antibody to CXCR4 or CXCL12 inhibited proliferation, a finding that suggests that CXCR4 gene is required to prevent apoptosis following serum withdrawal [103,104]. Similarly, systemic administration of CXCR4 antagonists inhibits the growth of intracranial glioblastoma and medulloblastoma xenografts by increasing apoptosis and decreasing the proliferation of tumor cells [105].

In patients with colorectal cancer and melanoma, CXCR4 expression in primary tumor cells correlates with recurrence, metastasis, and survival [106]. Interestingly, in these cancer patients, the rate of bone metastasis is not as high as that of prostate and breast cancers suggesting that CXCL12/CXCR4 may not be the only mechanism required for the establishment and localization of tumors to the marrow [91,107,108]. Moreover, in some

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instances CXCR4 may not be responsible for invasion but rather is critical for the outgrowth of micrometastases [109].

CXCR4 and CXCR7 were both identified in rhabdomyosarcoma (RMS) cells, which play overlapping and distinct roles in regulating metastatic behavior [110,111]. CXCR4 was more highly expressed on the more metastatic alveolar RMS (ARMS) cell lines than on the less metastatic lines derived from embryonal RMS (ERMS) [111], yet the expression of CXCR7 is inverse [110]. Although CXCL12 did not affect proliferation or survival of these cell lines through CXCR4 or CXCR7, migration, chemotaxis and adhesion was often observed [111]. In other findings, it was observed that hypoxia enhances both CXCR4 and CXCR7 promoter activity and receptor expression in ERMS cells [112]. Moreover, CXCR7 RMS cells responded to CXCL12 and CXCL11 in the presence of CXCR4 antagonists (T140, AMD3100). Animals injected with RMS cells which overexpressed CXCR7 experienced increased seeding efficiency of the tumor cells into bone marrow, whereas CXCR7 down-regulation showed had the opposite effect. Thus, both CXCL12/CXCR4 and CXCL12/CXCL11/CXCR7 axis are involved in the progression of RMS.

In contrast to solid tumors that invade into the marrow, most hematopoietic malignancies originate in the marrow. In this niche, hematopoietic malignancies cells are in close contact with marrow stromal cells that provide growth and survival signals through surface-bound or secreted factors. CXCL12/CXCR4 dependence has been demonstrated in acute leukemia, multiple myeloma, B-cell chronic lymphocytic leukemia, and cute myelogenous leukemia [113]. As a result, several studies are now underway to determine the therapeutic potential of CXCR4 antagonists in combination with other conventional therapies [102,114].

2.3.6 Tumor microenviroment (TME)—Tumors arise from cells that have sustained genetic mutations resulting in deregulation of normal growth control mechanisms [115]. Research focused on the origins of cancer has identified that genetic mutations within tumor cells have resulted in the concept that neoplastic progression is a cell-autonomous process. However, it has become increasingly apparent that the microenvironment influences many steps in tumor progression [116]. Not only do the cancer cells interact with each other, they are also influenced by the extracellular matrix (ECM) and other microenvironmental cells including fibroblasts, endothelial cells, and inflammatory cells [116,117].

More increasing evidence suggests that the stroma actively contributes to the growth and invasion of malignant tumors [118–122]. In further support of this notion, it was recently suggested that of CXCL12 may play a critical role as a chemoattractant in cancer development possibly at the level of the tumor niche [123,124]. The data suggests that both CXCL12 expression by fibroblasts and CXCR4 expression on tumor cells, within hypoxic areas of tumors, trigger tumor cell growth, motility and invasiveness. Importantly, CAFs, but not normal fibroblasts, stimulate tumor progression through CXCL12 secretion. Interestingly, Begley et al. have demonstrated that fibroblasts derived from older men, express more CXCL12 than younger men, suggesting that prostate stroma of older men may be “primed” for PCa growth [122,123]. At the same time, CXCL12 from CAFs may induce the recruitment of endothelial progenitors, which allow for tumor angiogenesis [124]. Targeted metastasis to the marrow or other sites of high CXCL12 expression involves CXCR4 activation on circulating tumor cells that “hijack” the CXCL12/CXCR4 axis for homing to microenvironments. CXCL12 gradients attract CXCR4-positive tumor cells to marrow niches where marrow stromal cells secrete high levels of CXCL12. As a consequence, tumor cells can invade adjacent tissues, resulting in bone destruction [69,122,125].

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In addition, the stroma cells from specialized microenvironments actually modulate CXCR4 expression, which is responsible for tumorigenesis and tumor progression. Ao et al. indicated that elevated stromal TGF-β elicits epithelial CXCR4 expression, allowing stromal SDF-1 to activate Akt pathway in the epithelial cells, which might interact initially to contribute to tumor formation and to set up conditions that would predispose cells to further malignant progression. P-Akt can then contribute to a loss of the growth-inhibitory response to TGF-β by blocking Smad-dependent manner [126]. These findings suggest that relatively small changes in specific molecular signals can alter the manner in which cells see and respond to their microenvironment. It also indicates that both of TGF-β and CXCL12/SDF-1 pathways are linked paracrine arbiters of tumorigenesis in CAF-driven tumorigenesis *in vivo* [126]. Similarly, IL-5 and IFN-γ are released from stromal cells and act as differential mediators for CXCR4 expression in neuroblastoma (NB) cell lines, which is associated with tumor metastasis *in vivo* [127]. Obviously, the tumor and stroma cell interactions is truly reciprocal; while stroma cells may support tumors, tumor cells in turn modulate the microenvironments within which they inside. It is notable that cancer is a systemic disease, encompassing multiple components of tumor and stroma cells that are a prerequisite for tumor cell invasion and metastasis (Fig2).

3. Therapeutical targeting based on the chemokine axis

The CXCL12/CXCR4/CXCR7 axis is a potential target for therapeutics that blocks CXCL12/CXCR4 or CXCL12/CXCR7 interactions or which inhibit activities of downstream signaling. Currently, CXCR4 has been targeted by multiple antagonists, such as bicyclams (AMD3100), and T22, TN14003, CTCE-9908, ALX40-4C, which are analogues and peptides designed to the amino-terminal region of the chemokine, CXCL12.

Bicyclams are macrocyclic polyamines, were found to be potent and selective inhibitors of the X4 strains of HIV, a function that primarily depends on their affinity for CXCR4. Functional studies have shown that a strong and direct interaction occurs between CXCR4 and bicyclams without receptor internalization. This interaction inhibits CXCL12 binding and signaling through CXCR4 and is able to block the binding of the CXCR4 monoclonal antibodies at nanomolar concentrations. Bicyclams with an aromatic linker, for example, AMD3100, have also been demonstrated effectiveness in mobilization of $CD34^+$ stem cells from the bone marrow for autologous transplantation in patient with leukemia or lymphoma and has fewer side effects than any current protocols [128]. At present AMD3100 is being clinical used as an orphan drug for these patients..

TN14003 is derived from amidating the carboxy terminus of T140 and by substituting basic residues with nonbasic polar amino acids to reduce the total-positive charges of the molecule. Liang *et al.* investigated the role of synthetic antagonist 14-mer peptide (TN14003) in inhibiting metastasis in an animal model [77]. Their data suggest that TN14003 is not only effective in limiting metastasis of breast cancer via inhibiting migration, but it may also prove useful as a diagnostic tool to identify CXCR4 receptor positive tumor cells in culture and tumors in paraffin embedded clinical samples. CTCE-9908 has shown both inhibition of the primary tumor and anti-metastatic effects in animal models of melanoma, osteosarcoma, breast, and prostate tumors[129–131]. In PCa, CTCE-9908 delivered intraperitoneally was also associated with inhibition of VEGF and angiogenesis, and reduced recruitment of myeloid host cells [130].

ALX40-4C, an oligocationic peptide, was originally developed to mimic the basic domain of the HIV-1 transactivation protein Tat in order to inhibit HIV-1 replication through inhibition of the Tat–Tar complex [132]. However, its main inhibitory effect is at the level of viral entry. This inhibition is due to its selective binding to the second extracellular loop of

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CXCR4 and abrogation of its use as a co-receptor for CXCR4-specific strains of HIV. ALX40-4C inhibits HIV-1 infection of T cell lines at nanomolar concentrations and also inhibits CXCL12 binding to CXCR4 at micromolar concentrations.

Based on observations as to the role of CXCR7 in progression and metastasis of several tumor types, therapies to block CXCR7 have been developed. Some small molecular inhibitors such as CCX733 or CCX266, siRNA, and blocking antibodies are already employed in experimental models *in vitro* and *in vivo* [61]. Yet the ability of CXCL12 to activate CXCR7 as well as CXCR4, raises some doubts as to whether the "selective blockage" of CXCR4 by T140 or AMD3100 without simultaneous blocking of CXCR7 will be effective. In fact, blockage of CXCR4 only partially inhibited responsiveness of tumor cells to CXCL12 gradients in several animal models [99,133,134]. Findings in our group also indicate that targeting of CXCR4 alone without simultaneous blockage of CXCR7 is likely to be an inefficient strategy for inhibiting CXCL12-mediated prometastatic responses of PCa cells (Unpublished data), suggesting that it may be more efficient to block some shared signaling molecules common to both receptors.

The development of a number of potent inhibitors of the CXCL12/CXCR4/CXCR7 axis, which have low toxicity, has opened the possibilities that investigations to disrupt this axis will have therapeutic benefit. While most studies are still in their infancy, there is great hope that agents that modulate the CXCL12/CXCR4 or CXCL12/CXCR7 axis will be useful in clinics. Importantly, the use of CXCR4/CXCL12 inhibitors in the treatment of cancer has produced some encouraging preclinical data. However, to be truly effective, a greater understanding of the role of CXCL12 and CXCR4 or CXCR7 in tumorigenesis and their other functions is required.

4. Conclusions

CXCL12 is primarily thought to regulate hematopoietic stem cell migration into and out of the bone marrow. CXCL12 is widely expressed in many tissues throughout development [135] and serves as a powerful chemoattractant for hematopoietic cells, where it facilitates their transmigration through endothelial cell barriers [136]. CXCL12 secretion by stomal cells in the tumor microenvironment is thought attract cancer cells via stimulation of the CXCR4 receptor that is up-regulated by tumor cells. CXCL12/CXCR4 activation regulates the pattern of metastatic spread with organs expressing high levels of CXCL12 developing secondary tumors (i.e., the bone marrow compartment). CXCL12 has a wide range of effects in regards to tumor development but the primary role of CXCL12 appears to be the facilitation of metastasis or mobilization of tumor cell, the recruitment of hematopoietic cells and perhaps the establishment of the cancer stem-like cell within the tumor microenvironment where high levels of CXCL12 recruit a highly tumorigenic population of tumor cells and promotes cell survival, proliferation, angiogenesis, and metastasis.

In contrast, CXCR7, the second CXCL12 receptor, may not induce Gαi-dependent calcium flux and receptor internalization. Similar to CXCR4, CXCR7 also serves as a co-receptor for several HIV strains and SIV, however, CXCR7 may not be crucial for trafficking of hematopoietic stem cells since its expression on $CD34^+$ cells is very low. Notably, our group and others have demonstrated that CXCR7 is involved in tumor cell growth, survival, and metastasis in many several tumor types. It is highly expressed on tumor-associated vasculature and may have an important role in tumor neovascularization. Blockade of CXCR7 could potentially be employed simultaneously with CXCR4 blockage in the inhibition of CXCL12-dependent tumor progression and metastasis, which may offer the better therapeutic effect in cancer treatment.

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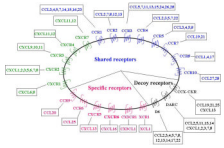

Figure 1. Chemokine family and their cognate receptors

Most chemokines can bind multiple receptors, and a single receptor can bind multiple chemokines. As shown in this case for most CC (green) and CXC (blue) chemokines. Decoy receptors (black) can also interact with multiple chemokines. By contrast, a minority of receptors (red) have only one ligand.

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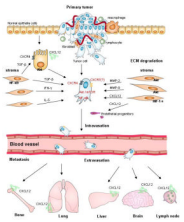

Figure 2. Schematic representation showing the role of microenvironment in tumor cell CXCR4 receptor activation in both the primary and metastatic sites

Molecular cross-talks between stroma and tumor cells in microenviroment may upregulate CXCR4 expression, which involve in tumorigenesis, and tumor cell intravasation. By CXCL12 gradients chemoattrcting of organ secretion, CXCR4-positive tumor cells in circulation may be responsible for the process of extravasation, and organ-specific metastasis. Abbreviation: CXL12 (SDF-1), stroma-derived factor; TGF-β, transforming growth factor-β; ECM, extracellular matric; IFN-γ, interferon-γ; NF-κB, nuclear factor κB; MMP-2,9, matrix metalloproteinase-2,9.

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