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Chemokine Receptor CXCR4 as a Therapeutic Target for Neuroectodermal Tumors

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Abstract

Chemokines (chemotactic cytokines) are a family of proteins associated with the trafficking and activation of leukocytes and other cell types in immune surveillance and inflammatory response. Besides their roles in the immune system, they play pleiotropic roles in tumor initiation, promotion, and progression. Chemokines can be classified into four subfamilies of chemokines, CXC, CC, C, or CX3C, based on their number and spacing of conserved cysteine residues near the N-terminus. This CXC subfamily can be further subclassified into two groups, depending on the presence or absence of a tripeptide motif glutamic acid–leucine–arginine (ELR) in the N-terminal domain. ELR$^-$CXCL12, which binds to CXCR4 has been frequently implicated in various cancers. Over the past several years, studies have increasingly shown that the CXCR4/CXCL12 axis plays critical roles in tumor progression, such as invasion, angiogenesis, survival, homing to metastatic sites. This review focuses on involvement of CXCR4/CXCL12 interaction in neuroectodermal cancers and their therapeutic potentials. As an attractive therapeutic target of CXCR4/CXCL12 axis for cancer chemotherapy, development history and application of CXCR4 antagonists are described.

Keywords

chemokine; chemokine receptor; CXCR4; CXCL12; SDF-1

1. Introduction

Chemokines are a superfamily of small secreted cytokines that induce cytoskeletal rearrangements and directional migration of several cell types through their interaction with G-protein-coupled receptors [1-3]. They are small peptidic ligands involved in the trafficking of leukocytes and other motile cells [4, 5]. These secreted proteins act in a coordinated fashion with cell-surface proteins, including integrins, to direct the specific homing of various subsets of hematopoietic cells to specific anatomical sites [6-9]. They

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play a major role in regulating the migration of cells of the immune system, leading to modulation of immune responses[10, 11].

The primary role of chemokines/receptors is to regulate the recruitment and trafficking of leukocyte subsets to inflammatory sites. This action is achieved through chemoattraction by activating leukocyte integrins that bind to their adhesion receptors on endothelial cells [12, 13]. Chemokines are also involved in neuronal cell migration and patterning [14]. Chemokines bind within the extracellular domain of the chemokine receptors, which comprises the N-terminus and three extracellular loops [15]. Upon activation, their intracellular domain, which consists of three loops and the C-terminus, drives dissociation of G-protein heterotrimers into α and βγ subunits. This action leads to events such as inhibition of adenylyl cyclase activity [15, 16]. Activation of these effectors leads to functional outcomes induced by chemokine receptor signaling (Figure 1) [17-19]. Typical cellular consequences of chemokine binding include changes in gene expression, cell polarization, and chemotaxis (directed cell migration) [20]. Their exact role depends on the expression pattern of receptors on specific leukocyte subsets [5] but encompasses the regulation of lymphocyte trafficking, lymphoid tissue development, Th1/Th2 modulation and the effecting of inflammatory reactions. Chemokine receptors are also found on other cell types, and play a part in stem cell recruitment, angiogenesis, development and wound healing [20]. Recent studies suggest that many cancers express an extensive network of chemokines and chemokine receptors [21, 22]. These tumors are characterized by deregulation of chemokines and abnormal chemokine receptor expression.

Interest in chemokines/chemokine receptors in the neuroectoderm has been rapidly increasing due to their involvement in a diverse range of neurological diseases. Concordantly, the volume of literature pertaining to the involvement of chemokines and chemokine receptors in neuroectoderm development has been growing rapidly in recent years [23]. During neurological diseases, the expression of chemokines can be selectively induced or upregulated in a wide range of cells, including microglia, astrocytes, neurons, and endothelial cells [12, 24]. As such, these molecules—both chemokines and chemokine receptors—represent potential therapeutic targets.

2. Classifications of chemokines and their receptors

Chemokine receptors are G protein-coupled receptors (GPCRs) with seven-transmembrane domains that are highly conserved in evolution [25-27]. By binding to their corresponding receptors, chemokines activate a series of downstream signaling pathways to guide the movement of leukocytes to target tissues or organs [28]. Directional movement of leukocytes through a concentration gradient of chemokine is defined as “chemotaxis”. Chemokines can be classified into four subfamilies of chemokines, CXC, CC, C, or CX3C, based on their number and spacing of conserved cysteine residues near the N-terminus [3, 4, 15] (Figure 2A). CXC, CC, and CX3C chemokines all have four conserved cysteines, whereas C chemokines have only two. CXC and CX3C chemokines are distinguished by the presence of one (CXC) or three (CX3C) amino acids between the first and second cysteines, whereas the first two cysteines of CC chemokines are adjacent. The nomenclature of chemokines (e.g., ‘CXCL1’) is comprised of their subclass (CXC, CC, etc.) followed by “L” for ligand, and a specific number [4, 5]. This CXC subfamily can be further subclassified into two groups, depending on the presence or absence of a tripeptide motif glutamic acid–leucine–arginine (ELR) in the N-terminal domain (Figure 2B). The ELR presence has been proposed to relate to the functional correlation of structural characteristics of CXC chemokines, such as specificity for neutrophil chemotaxis and angiogenesis [29-33]. The ELR-containing chemokines (such as IL-8, GRO, and ENA-78) have a uniform function as neutrophil chemoattractants and activators. They have also been reported to induce

angiogenesis and to be chemotactic for endothelial cells. In contrast, the non-ELR-CXC chemokines (such as PF-4, IP-10, MIG, and CXCL12) show disparate activities. They are themselves nonangiogenic and are even known to possess anti-angiogenic properties. One exception is CXCL12, which induces neovascularization [33, 34]. In general, the members of each chemokine subfamily show overlapping specificities. For instance, the CXC-ELR1 chemokines are chemoattractants for neutrophils, but not for monocytes. However, CXC-ELR2 chemokines attract lymphocytes and monocytes but are poor chemoattractants for neutrophils. So far, 53 human chemokines and 23 chemokine receptors have been cloned or characterized (http://cytokine.medic.kumamoto-u.ac.jp/).

3. History of CXCR4/CXCL12 and the functions in the normal neuroectoderm

A *CXCL12* cDNA clone was first isolated by Tashiro et al. from a murine bone marrow stroma cell line by the signal sequence trap method. The gene was originally named stromal cell-derived factor-1 (*SDF-1*) [35]. A few years later, two groups identified its receptor, an orphan GPCR called LESTR/fusin [36, 37]. LESTR/fusin was also identified as the co-receptor for human immunodeficiency virus (HIV-1) infection of CD4+ lymphocytes [38]. CXCL12 was shown to inhibited infection by T-tropic HIV of HeLa-CD4 cells [36, 37]. Because of its reactivity to CXCL12, the nomenclature was revised and LESTR/fusion was replaced by CXCR4. CXCR4/CXCL12 plays pleiotropic functions in the peripheral immune system. Bleul et al. also reported that CXCL12 is a highly efficacious chemoattractant for lymphocytes and monocytes, but not neutrophils [36]. In addition, Klein et al. reported that CXCR4/CXCL12 not only regulates the development of T and B lymphocytes but also contributes to the survival of mature lymphocytes and to the generation of memory T cells [39]. Later studies have indicated that CXCR4/CXCL12 enhances the inflammatory infiltration of neutrophils or lymphocytes in diverse models and settings involving acute inflammation or fulminant infection [40-42]. Most importantly, CXCL12 is a major regulator for the homing of hematopoietic progenitor cells to the bone marrow microenvironment [43]. Deficient development of blood cells and the heart were also described in CXCL12 knockout mice [44]. Identical phenotypes were also observed in knockout mice for its receptor, CXCR4 [45, 46], suggesting that the interaction between CXCL12 and CXCR4 may be the “key and lock” pair relationship. Only recently, a new receptor, CXCR7, was reported as an alternative non-signaling CXCL12 receptor, suggesting that the CXCR4/CXCL12 relationship is not entirely exclusive [47]. However, CXCR7, unlike CXCR4, is only expressed in limited tissues, and needs further studies to determine its role.

The interplay between CXCL12 and CXCR4 is critical to normal development. Unlike mice deficient in other chemokine/receptors, mice lacking CXCL12 or CXCR4 die in uterus or shortly after birth [4, 44-46, 48]. CXCR4/CXCL12 signaling is required during the development of the hematopoietic, cardiac, vascular, muscular, and nervous systems. Absence of CXCR4/CXCL12 axis in embryonic life leads to defects in bone marrow myeloid cell formation, cardiac function due to impaired ventricular septum formation, and developmental defects in the cerebellum and in the vasculature of the gastrointestinal tract [44-46].

The expression of CXCL12 and its receptor, CXCR4, has been described in neuronal, astroglial, and microglial cells [14, 49]. CXCL12 exerts its chemotactic action to direct organogenesis and tissue structure in the developing brain. This is demonstrated by studies of both CXCL12−/− and CXCR4−/− knockout mice, in which gene deletion resulted in significant abnormalities in cerebellar and hippocampus development such as a misplaced external granule cell layer and clusters of proliferating granule cell precursors [44, 46,

50-54]. Thus, evidence is accumulating that the CXCR4 plays a crucial role in normal development of the cerebellar cortex and in cell cycle control of neuronal precursors within the external granule cell layer.

4. Pleiotropic roles of CXCR4 in various types of cancers

CXCR4 is the most widely expressed chemokine receptor in many different cancers. The effects of CXCL12 on CXCR4-bearing tumor cells include a wide diversity of functions such as angiogenesis, invasion, locomotion, extravasation, directional migration, homing, and cell survival (see reviews: [55-59]). Among these, the function of controlling cell migration and homing, which is the rate-limiting step of multistep processes of metastasis, is unique for CXCR4/CXCL12. The precise mechanisms determining the directional migration and invasion of tumor cells into specific organs remained elusive for a long time [59, 60]. The CXCR4 chemokine receptor mediates the migration of human stem cells to marrow and possibly peripheral blood cells to lymph nodes and spleen by the binding of its ligand, CXCL12 [61-68]. The process of metastasis is similar to leukocyte and stem cell trafficking, processes which utilize the CXCR4/CXCL12 axis [69]. Cancer cells that express CXCR4 exploit the same signaling pathway leading to homing and retention in tissues with enriched CXCL12. When CXCL12 binds to CXCR4, the complex activates $G\alpha_i$-protein-mediated signaling (pertussis toxin-sensitive) [70], including downstream signal pathways such as Ras/MAP Kinases and phosphatidylinositol 3-kinase (PI3K)/Akt in lymphocyte, megakaryocytes, and hematopoietic stem cells [16, 36, 71-75]. The interaction of CXCR4 and CXCL12 has been shown to induce the activation of the PI3K/Akt signaling pathway. Also, PI3K activation is in turn closely correlated with cell motility and migration. Akt plays a critical role in promoting cell survival by phosphorylating and inactivating components of the apoptotic machinary, such as BAD, caspase-9, focal adhesion kinase (FAK), and FKHRL1.

Müller et al. published a landmark study on the involvement of CXCR4 in breast cancer metastasis [76]. In samples collected from various breast cancer patients, they found that the level of expression of CXCR4 is higher in primary tumors relative to normal mammary glands or mammary epithelial cells. In contrast, CXCL12 is highly expressed in the most common destinations of breast cancer metastasis, including the lymph nodes, lung, liver, and bone marrow. The CXCR4/CXCL12 axis has been demonstrated to play critical roles in the metastasis of various types of cancers as listed in Table 1. Liang et al. demonstrated that silencing CXCR4 by RNA interference technology prevented tumorigenesis in an animal model of breast cancer metastasis [77]. Furthermore, decreasing expression levels of CXCR4 by microRNA against CXCR4 also reduced migration and invasion *in vitro* and lung metastases *in vivo* [78]. MicroRNAs have been shown to function as regulatory molecules and to play an important role in cancer progression (for reviews, see: [79, 80]). These data support the possibility that small interfering RNA or microRNA against CXCR4 can serve as an alternative means of lowering CXCR4 expression to block subsequent invasion and metastasis. Taken together, these studies confirm the necessity of CXCR4 in breast cancer metastasis and suggest a novel preventive and therapeutic strategy for cancer management.

Various studies have shown significant CXCL12 concentrations in the fluid-filled cavities through which many cancers disseminate and at tissue locations in which metastases characteristically develop. Furthermore, CXCL12:CXCR4 can promote cancer dissemination indirectly by enhancing the vascular supply, since the CXCR4/CXCL12 axis may also promote tumour angiogenesis. CXCL12 influences the interaction of CD34+ hematopoietic cells with the hematopoietic microenvironment by regulating their migration and adhesion as well as the secretion of vascular endothelial growth factor (VEGF) [81-84].

On the one hand, CXCL12 has been shown to induce secretion of VEGF in lymphohematopoietic $CXCR4^+$ cell lines [72]. In this study, the authors showed that the VEGF protein levels increased in conditioned medium of cell lines treated with CXCL12. While the other hand, VEGF increased CXCL12 expression in endothelial cells [85], and anti-CXCR4 antibody disrupted extracellular matrix-dependent endothelial cell tube formation *in vitro*. This morphogenic process is closely associated with CXCR4 expression. Pertussin toxin (inhibitor of $G\alpha_i$) and neutralizing antibodies of CXCL12 inhibited bFGF (basic fibroblast growth factor) and VEGF-dependent neovascularization *in vivo*. The fact that blocking either CXCR4/CXCL12 interaction or the major G-protein of the CXCR4/CXCL12 signaling pathway ($G\alpha_I$) inhibits VEGF-dependent neovascularization, strongly suggests that CXCR4/CXCL12 indeed regulates VEGF-dependent angiogenesis. These results indicate that CXCR4/CXCL12 regulates VEGF-regulated autocrine signaling systems, which in turn are essential regulators of endothelial cell morphogenesis and angiogenesis [86-89]. The role of CXCR4/CXCL12 in tumor angiogenesis *in vivo* was demonstrated in a squamous cell carcinoma of the head and neck (SCCHN) orthotopic animal model using highly metastatic subclones generated via *in vivo* selection of SCCHN cells through four rounds of serial metastases [90]. They showed that anti-CXCR4 treatment suppressed primary tumor growth by inhibiting tumor angiogenesis. Liang et al. also reported that CXCR4/CXCL12 induced Akt phosphorylation, which resulted in upregulation of VEGF at both the mRNA and protein levels, because blocking the activation of Akt signaling led to a decrease in VEGF protein levels induced by CXCR4/CXCL12 axis [91]. In addition, blocking CXCR4/CXCL12 interaction with a CXCR4 antagonist suppressed tumor angiogenesis and growth *in vivo*. Furthermore, VEGF mRNA levels correlated well with CXCR4 mRNA levels in patient tumor samples. Thus, their study demonstrates that the CXCR4/CXCL12 signaling axis can induce angiogenesis and progression of tumors by increasing expression of VEGF through the activation of the PI3K/Akt pathway.

In colorectal cancer, CXCR4 is abundantly expressed in various colorectal carcinoma cells and elevated CXCR4 expression is associated with disease progression and reduced survival in patients [92-98].

Increasing evidence suggests that stem cells may play a crucial role in cancer progression such as tumor initiation, growth, and metastasis [99-103]. Hermann et al. reported the involvement of cancer stem cells in pancreatic cancer [104]. Pancreatic cancer has a poor prognosis of a 5-year survival rate of 1 – 4 % and a median survival of 4 – 6 months [105]. By using two biomarkers for cancer stem cells, CD133, a well-established marker for cancer stem cell for brain tumors, and CXCR4, they demonstrated that a subpopulation of CD133+CXCR4+ was responsible for metastatic process as well as resistance to standard chemotherapy. Taken together, strategies aiming CXCR4/CXCL12 axis may have important clinical application to inhibit cancer progression in numerous cancer types.

5. CXCR4 and neuroectodermal cancer

5.1. CXCR4 in neuroblastoma

Neuroblastoma is the second most common solid tumor found in children, originating from precursors derived from embryonic neural crest cells that form the peripheral sympathetic nervous system with a high potential to migrate. About one-half of children have localized tumors that can be cured with surgery alone, while the remaining children have widespread metastatic disease or quite large, aggressive, localized tumors. The latter have a poor long-term survival rate of approximately 30%. Despite advances in combined therapies, the survival rate of patients with metastatic neuroblastoma has not significantly improved over the last decade. Therefore, there is an urgent need for genetic and biologic markers for the diverse clinical phenotypes observed in neuroblastoma patients. One of the emerging

biomarkers in neuroblastoma is the overexpression of the CXCR4. CXCR4 expression correlates with high-stage disease [106], and the interactions of CXCR4 by CXCL12 was shown to be necessary for the survival of several neuroblastoma cells *in vitro* [107]. Vasudevan et al. [108] reviewed the prognostically significant molecular biomarkers of high risk neuroblastoma and found that CXCR4 is one such marker. A higher expression of CXCR4 was found in primary neuroblastoma cells from patients with high-stage disease and in patients with bone and bone marrow metastases [106]. Disease-free survival in patients with tumors expressing high levels of CXCR4 is significantly worse than in patients with low CXCR4 tumor expression. Geminder et al. [109] investigated the expression levels of CXCR4 in various NB cell lines. Using CXCR4-expressing SH-SY5Y cells, they found that CXCL12 induces the migration of CXCR4-expressing neuroblastoma cells in CXCR4- and G protein-dependent manners. SH-SY5Y cells interacted at multiple levels with bone marrow components so that bone marrow-derived constituents promote SH-SY5Y cell migration, adhesion to bone marrow stromal cells, and proliferation. These results suggest that SH-SY5Y neuroblastoma cells are capable of homing to the bone marrow and that the ability of neuroblastoma tumors to preferentially form metastases in the bone marrow may be influenced by CXCR4/CXCL12 interactions. Moreover, Zhang et al. [110] screened chemokine/receptor profiles in different neuroblastoma cell lines and investigated the roles of CXCR4 in neuroblastoma tumor growth and progression using mouse xenograft models. They demonstrated the important role of stromal cells in neuroblastoma metastasis and a potential regulatory tumor-host mechanism for CXCR4 in neuroblastoma. Several studies further demonstrated that CXCR4 expression can be regulated positively by cytokines such as TGF-β1, VEGF, and bFGF. CXCR4 expression can also be regulated negatively by cytokines such as IL-5 and IFN-α in leukocytes, endothelial cells, and neural cells [34, 111-114]. In addition, hypoxia was shown to strongly affect the chemokine system in macrophages [115]. Overexpression of CXCR4 promoted neuroblastoma cell migration selectively toward bone marrow stromal cell conditioned medium *in vitro* [110]. In a mouse xenograft model, bone marrow metastasis could be achieved by CXCR4 overexpression. Furthermore, Chen et al. [116] suggested the regulation of angiogenesis by CXCR4 in neuroblastomas and that the dissemination of CXCR4-overexpressed neuroblastoma cells from primary tumors could result from increased neovasculatures [110].

5.2. CXCR4 in medulloblastoma

Medulloblastomas are the most common malignant brain tumors in childhood with a median age of onset at 9 years [117]. Medulloblastomas are histologically divided into 4 major subgroups. While classic and desmoplastic tumors account for the vast majority of cases, medulloblastomas with extensive nodularity and large cell medulloblastomas are rare [118]. All medulloblastoma subtypes are believed to be originated from neural progenitors of the cerebellum, although, the exact cellular origin remains to be elucidated in most cases.

CXCR4 is strongly expressed in proliferating granule cell precursors [39, 119]. CXCL12, which is segregated by meningeal cells of the leptomeninx, significantly enhances cell proliferation [119]. This effect is reduced by blocking the CXCR4 receptor either by AMD 3100 or pertussis toxin. This indicates coupling of neuronal CXCR4 to Gαi, which has previously been demonstrated to be expressed in granule cell precursors [120, 121]. The involvement of CXCR4 in medulloblastomas was first reported by Rubin et al. [120], who used a desmoplastic medulloblastoma cell line for both *in vitro* experiments and *in vivo* tumor models. Their study has shown that CXCR4 mRNA and protein are expressed at high levels in brain tumors of both neuronal and astrocytic lineage. The ligand CXCL12 is expressed in tumor-associated blood vessels and/or tumor cells, suggesting a paracrine relationship for CXCR4 activation *in vivo*. *In vitro*, CXCL12 exerts proliferative, antiapoptotic, and chemotactic effects on medulloblastoma cell lines.

Schuller et al. [122] examined the expression pattern of the CXCR4 receptor in 90 cases of tumor specimens, including classic medulloblastoma, desmoplastic medulloblastoma, and medulloblastoma with extensive nodularity. In this study, they found that a small subset of medulloblastomas carry mutations in the gene encoding the CXCR4. While overexpression of CXCR4 is dominant in most cases of cancers, CXCR4 mutation is rarely reported. However, Schuller et al. described 2 cases of medulloblastomas carrying mutations in the CXCR4 gene [122]. The A157C mutation is located in the first transmembrane section and the C414T mutation is located in the second transmembrane region, a part of the receptor which is relatively close to the cell surface and possibly important for binding of its ligand [123]. They speculated that mutations within the first and second transmembrane regions might contribute to pathologic receptor activity or to resistance to inhibitors such as AMD 3100. Moreover, strong expression of CXCR4 mRNA was demonstrated in medulloblastomas that likely derive from the cerebellar external granule cell layer. These data suggest that CXCR4 may be responsible for the development of specific medulloblastoma subtypes. Furthermore, expression of CXCR4 could be an improved detection means of tumors derived from the cerebellar external granule cell layer over classical histology and silver staining.

CXCL12 could also contribute to the pattern of medulloblastoma spread. Medulloblastoma is distinctively different from other brain tumors because it often metastasizes to bone and liver tissues in which CXCL12 are enriched in their stromas. Therefore, CXCR4 may play a critical role in a small subtype of medulloblastomas for their growth and metastasis.

5.3. CXCR4 in other neuroectodermal tumors

Melanoma preferentially metastasizes to the lung, liver and brain, that are sites of breast cancer metastasis[124]. High expression of CXCR4, CCR7 and CCR10 was observed in malignant melanoma cell lines and melanoma cells as compared with normal primary melanocytes[76,125,126]. Transduction of B16 melanoma cells with CXCR4 increased pulmonary metastasis by i.v. and s.c. inoculation of tumor cells[127], indicating that organ-specific metastasis of melanoma is mediated by CXCR4. The increase of pulmonary metastasis was supresses by treatment with CXCR4 antagonists [127,128]. It was demonstrated by two independent groups that primary melanoma expressing CXCR4 is related to a higher incidence of metastases and a highly motality rate[129,130], suggesting CXCR4 could be a useful biomarker for predicting metastatic melanoma in patients as well as the therapeutic target in melanoma.

Small cell lung cancer (SCLC) is also one of the aggressive and rapidly metastasizing neoplasms. Due to the widespread metastasis and resistance against chemotherapeutic drugs, two-year survival rate of patients is extremely low[131,132]. SCLC cell lines and primary tumor sample from SCLC patients express CXCR4 on the cell surface[133,134]. Kijima et al. reported that functional expression of CXCR4 receptor is involved in the pathogenesis of SCLC in vivo [133]. CXCL12 increased cell motility, adhesion, and formation of filopodia and neurite-like projections of CXCR4-expressing SCLC cells. CXCL12-induced integrin activation mediates adhesion of SCLC cells to extracellular matrix such as VCAM-1, fibronectin and collagen [134,135]. This is mediated by co-operation of CXCR4 and integrin signaling. Increased adhesion of SCLC cells to stromal cells protects from the chemotherapy-induced apoptosis to confer chemoresistance. Accordingly, CXCR4 antagonists would be useful to overcome CXCL12-mediated adhesion survival signals in the microenvironment of SCLC.

6. Potential therapeutics targeting CXCR4

6.1. Peptide-based CXCR4 antagonists

CXCR4 is a major co-receptor for T-cell line-tropic (T-tropic) HIV infection and, thus, numerous compounds targeting CXCR4 have been developed and reported as HIV entry inhibitors in recent years. T22 is the first potent anti-HIV peptide, which was designed from horseshoe crab-derived anti-microbial peptide, polyphemusin II [136]. Although the molecular target of T22 had not been originally identified, Murakami *et al* reported the anti-HIV activity was derived from the inhibition of CXCR4 [137], which was reported to be a second receptor for HIV-1 infection [36, 37]. T22 specifically inhibits T-tropic HIV-1 infection, but not macrophage-tropic strain. ALX40-4C is also a polycationic anti-HIV peptide, which prevents the viral binding on CXCR4 [138]. Tamamura *et al* reported a landmark development of a specific CXCR4 inhibitor, T140 [139] through structure-activity relationship study [140] and down-sizing study [141, 142] of T22. T140 is a 14-residue peptide that possessed high levels of anti-HIV activity and antagonism of T cell line-tropic HIV-1 entry as compared to other antagonists of CXCR4 that existed in 1998. This peptide exerts inverse agonistic activity, while AMD3100 is a weak partial agonist [143]. The compound was further improved by amidating the C-terminus of T140 and reducing the total number of positive charges by substituting basic residues with non-basic, polar amino acids to generate TN14003, which is less cytotoxic and more stable in serum compared to T140 [144]. The concentration of TN14003 required for 50% protection of HIV-induced cytopathogenicity in MT-4 cells is 0.6 nM in contrast to 410 μM leading to 50% toxicity. These results reflect an excellent therapeutic index for TN14003 (Safety index, $SI_{TN14003}$=680,000) as well as a compelling therapeutic opportunity for a new inhibitor of CXCR4. Further optimization and N-terminal acylation of TN14003 led to development of the biostable analogue 4F-benzoyl-TN14003 (TF14016), which possess highly potent anti-HIV activity as well as CXCR4 antagonistic activity [145, 146]. Two groups independently evaluated the efficacy of TN14003 in inhibiting metastasis in an animal model [147, 148]. They confirmed that blocking CXCR4 was effective in limiting metastasis of breast cancer. Numerous investigators have used T140 analogs as proof of principal to study the effect of CXCR4 blocade [128, 149-152]. Several labeled T140 derivatives including biotin, fluorescent chromophores [153, 154] and radioisotope [155] have also been developed, which would be applicable to metastatic cancer diagnosis. T140 analogs provide a compelling efficacy benchmark with which to compare future generations of drug candidates.

A new class of peptides and peptidomimetics has been reported that was converted from these T140 analogs with better phamaceutical properties than peptides. Fujii et al. reported that cyclic pentapeptide FC131 (Figure 3, **1**) exerts anti-HIV activity as well as CXCR4 antagonist activity equipotent to T140 [156]. Using orthogonal peptide library strategy, pharmacophore residues in the close proximity, which were identified by a structure-activity relathionship study [157, 158] and conformational analysis [159] of T140, are embedded on the cyclic peptide template. It is noteworthy that even one-third molecular-size reduction of T140 could reproduce both CXCL12-binding inhibition to CXCR4 as well as CXCR4-mediated HIV-1 infection. FC131 analogues having retro-inverso sequence [160] or *N*-methyl amino acid [161] are also potent CXCR4 antagonists. Design of pseudopeptides containing peptide backbone mimetics of FC131 was attempted; however, most of the compounds showed similar or less potent bioactivity compared with FC131 [162-165]. Recently, DeMarco has reported a novel CXCR4 antagonist, POL3026 [166]. POL3026 was designed by head-to-tail cyclization of TC14003 [158] based on the β-hairpin protein epitope mimetic (PEM) design concept, posseting high potency and favorable pharmacokinetic properties [167].

6.2. Small molecule CXCR4 antagonists

The poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of peptide inhibitors typically limit their clinical use due to low bioavailability. To mimic a peptide with a small non-peptide drug remains a major goal of medicinal chemistry programs. To date, a modest number of reports have appeared in the literature describing efforts to develop selective, non-peptidic, small molecule antagonists of CXCR4.

The cyclams and bicyclams are a class of non-peptide molecules that have been shown to demonstrate antagonist activity against the CXCR4 receptor, and these have dominated literature research publications [168]. The most notable compound from this class is AMD3100 (Figure 3, **2**), which has a partial agonistic activity [169]. It is a symmetrical molecule that contains two cyclam subunits linked by an aromatic tether and shows a high degree of specificity for CXCR4 as opposed to other chemokine receptors [170]. It exhibits inhibitory activity against several strains of T-tropic HIV, but suffers poor oral bioavailability and must therefore be administered via intravenous or subcutaneous injection [170-172]. AMD3100 was advanced as far as Phase II clinical evaluation, where it demonstrated early evidence of anti-viral activity [170-172]; however, AMD3100 did not reduce viral load in HIV patients, while causing thrombocytopenia in one patient, premature ventricular contractions in two patients, and paresthesias in several patients [173, 174]. The cyclams (a structural class represented by AMD3100) are a well-known metal-chelating moiety and it is reasonable to presume that chelated metals may be playing a key role in the cardiac side effects that were observed with AMD3100 [175]. This presumption is reflected in the exclusion criteria outlined for a second generation tetrahydroquinoline-based compound, AMD070 (Figure 3, **3**), which has recently entered Phase I clinical evaluation as an anti-HIV agent [176].

Systemic administration of AMD3100 decreased the growth of GBM and medulloblastoma in an orthotopic animal model [177]. AMD 3100 treatment reduced activation of extracellular signal-regulated kinases 1 and 2 (Erk 1/2) as well as Akt and also increased rates of apoptosis in both tumor types. Their studies suggest CXCR4 signaling is a critical component of brain tumor biology. Based on the abundant implication of CXCL12-CXCR4 axis in many physiological processes as well as the experience of AMD3100 in its HIV trial, safer drugs without potential side-effects are desired for the treatment of brain tumors. Currently, AMD3100 is being tested in the clinic for an indication of stem cell mobilization, which would only require a one time administration of the drug.

Several nonpeptide CXCR4 antagonists, having two aromatic amine moieties connected by a *para*-xylenediamine group, were reported. AMD3465 (Figure 3, **4**) is a monomacrocyclic CXCR4 antagonist, in which one cyclam unit of AMD3100 has been replaced with an *N*-picolyl group [178]. More effective inhibition of CXCL12-induced chemotaxis by AMD3465 as compared with AMD3100 indicates that eight basic amino groups are not needed for the CXCR4 antagonism. Bis(dipicolylamine)-*p*-xylene-Zn complex (Figure 3, **5**), which was originally designed as a molecular probe to recognize phospholylated peptide sequences [179], showed potent CXCR4 antagonistic activity [180]. A stable complex of the dipicolylamine moieties with zinc ion maintains the active structure. A recent note-worthy report on small molecule CXCR4 antagonists including WZ811 (Figure 3, **6**) conducted by Zhan et al. [154]. They designed a series of small molecules based on the structure-activity profile of AMD3100 vs. CXCR4 published by Trent et al. [169] and identified a lead via an affinity binding assay using TN14003 (a peptide–based CXCR4 antagonist) and subsequent functional assays using CXCL12 (cAMP and Matrigel invasion assays).

A series of small molecules containing pharmacophores of T140 and FC131 has been reported. Kureha has developed KRH1636 (Figure 3, **7**) based on the N-terminal fragment of

T140 [181]. KRH1636 does not contain a cyclam subunit, thereby avoiding the potential liability of metal ion encapsulation. From tripeptide library bearing three pharmacophores of the *N*-terminal region of 4F-benzoyl-TN14003 and 4F-benzoyl-TE14011, several potent CXCR4 antagonists have been identified [182]. Small molecules containing 3,6-dihydropyridin-2-one [183] and indole scaffolds [184] has been designed by scaffold-based approach using FC131 pharmacophores, which are expected to be lead molecules for structure-activity relationship study.

6.3. Miscellaneous

Chemokine fragment peptides reproduce the binding affinity to chemokine receptors as ligands and/or inhibitors. Crump et al. demonstrated the substitution of Pro2 of CXCL12 with Gly resulted in complete loss of receptor activation ability of CXCR4 with slightly weaker binding affinity with CXCR4 [185]. Loetscher et al. reported that N-terminal 9 residues of CXCL12 (1-9), and the dimeric peptide induce chemotactic and calcium responses at high concentration, while the P2G analogues show antagonistic activity for CXCR4 [186]. CTCE-9908 is a 17-mer peptide CXCR4 antagonist, which is a dimeric analogue of CXCL12 (1-8) having P2G substitution [187]. Treatment with CTCT-9908 decreased migration, invasion and the growth rate of osteosarcoma *in vitro*, and reduced the development of pulmonary metastases of osteosarcoma and melanoma cells *in vivo* [188]. CTCE-0214, a 31-mer analogue of CXCL12, in which the intervening sequence of CXCL12 is deleted and α-helix inducible cyclic structure is introduced, reproduces intracellular calcium mobilization induced by CXCL12 [189]. This agonistic peptide mobilizes human colony-forming cells (CFC) to spleen and peripheral blood [190], and synergizes with other cytokines on survival of stem and progenitor cells [191].

vMIP-II is a viral chemokine encoded by Kaposi's sarcoma–associated herpesvirus. vMIP-II binds CXCR4 with high affinity, and inhibits the calcium mobilization elicited by CXCL12 as well as HIV-1 infection [192]. The full length of vMIP-II is recognized both by CXCR4 and CCR5, N-terminal 21-mer fragment, vMIP-II (1-21), displays the antagonistic activity against CXCR4 [193]. Dimerized peptide of vMIP-II N-terminal 11-residue, named vMIP-II (1-11) dimer, is also a weak antagonist for CXCR4 [194]. Dong et al. reported that synthetically and modularly modified chemokine, in which N-terminal 8 residues of CXCL12 is replaced with all-D-isomer of N-terminal 10-mer fragment of vMIP-II, does not activate CXCR4, but is effective to block HIV-1 infection [195, 196].

7. Concluding remarks

Vast evidence indicates that cancer cells express the CXCR4 chemokine receptor and that its interaction with CXCL12 is crucial for tumor proliferation, migration, and angiogenesis. CXCR4/CXCL12 plays a central role in Paget's famous hypothesis of "seed-and-soil" [197], and thus modulating this CXCR4/CXCL12 axis may provide an alternative target for cancer therapy by blocking cancer progression. In addition, CXCR4 expression profiles can be utilized to determine different stages of malignancy in various cancers. This may lead to alternative prognostic markers for cancers and a strategy to enhance both diagnostic and therapeutic strategies. Numerous research articles validate the possibility of targeting CXCR4/CXCL12 interaction in tumor progression as not only a therapeutic approach, but also a chemopreventive strategy, blocking the cancer progression or malignant transformation.

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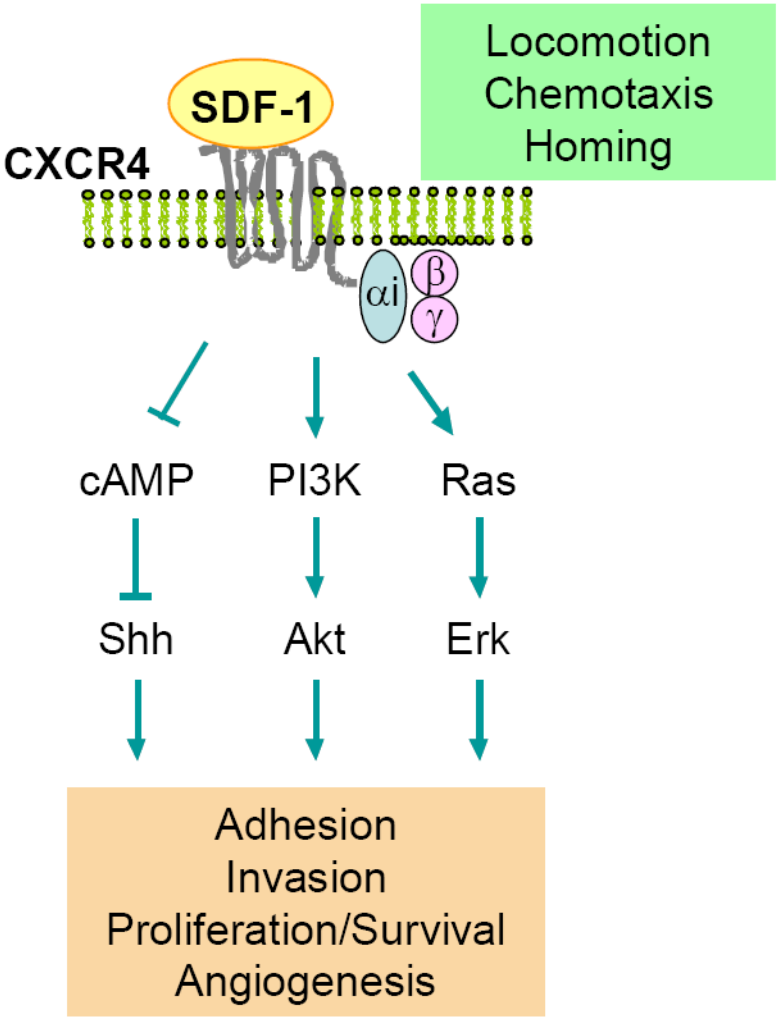
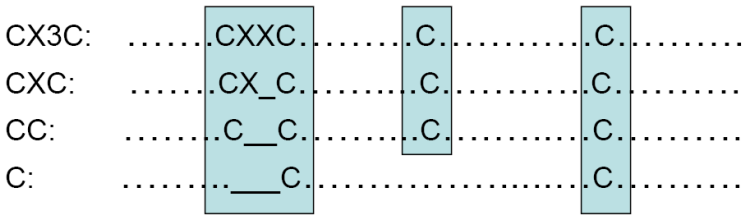


Figure 1.
CXCR4 as an example of chemokine receptor signaling. Stromal cell derived factor-1 (SDF-1) interacts with CXCR4. Binding of SDF-1 (CXCL12) to CXCR4 activates Gαi (pertussis toxin-sensitive) signaling pathways through which reduces cAMP signaling molecules in cells, and leads to phosphatidylinositol 3-kinase (PI3K)/Akt and Ras/MAPK signaling pathways. These signaling pathways include locomotion, chemotaxis, homing, adhesion, invasion and angiogenesis in lymphocytes, macrophages, neutrophils, hematopoietic stem cells, and cancerous cells.

A



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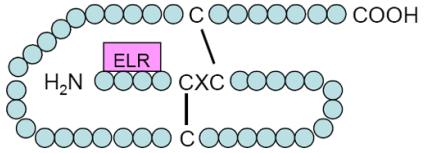

Subgroup	Official name	Synonyms	Receptor
ELR+	CXCL1	GROα	CXCR2
	CXCL2	GROβ	CXCR2
	CXCL3	GROγ	CXCR2
	CXCL5	ENA-78	CXCR1, CXCR2
	CXCL6	GCP-2	CXCR1
	CXCL7	NAP-2	CXCR2
	CXCL8	IL-8	CXCR1, CXCR2
	CXCL15	Lungkine	CXCR2
ELR-	CXCL4	PF-4	
	CXCL9	MIG	CXCR3
	CXCL10	IP-10	CXCR3
	CXCL11	I-TAC	CXCR3, CXCR7
	CXCL12	SDF-1	CXCR4, CXCR7
	CXCL13	BCA-1	CXCR5
	CXCL14	BRAK	
	CXCL16		CXCR6

Figure 2.

(A) Chemokines are classified into four major subfamilies according to the configuration of cysteine residues (http://cytokine.medic.kumamoto-u.ac.jp/). (B) CXC subfamily is further classified two subgroups depending on the presence or absence of the sequence motif glutamate-leucine-arginine (ELR) at the N-terminus. Individual chemokines can bind more than one chemokine receptors.

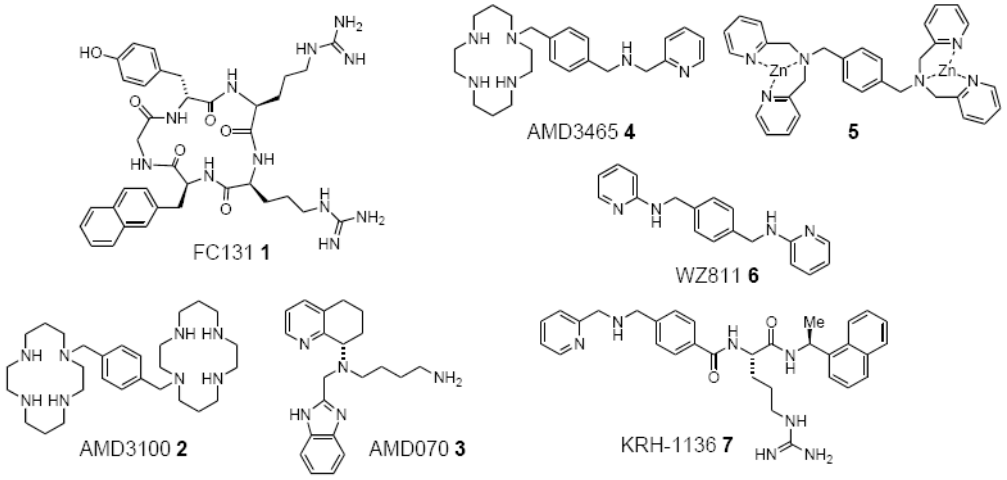

Figure 3.
Structures of CXCR4 antagonists.

Table 1

Literatures on the involvement of CXCR4 in various cancers

Cancer type	References
Breast cancer	Muller, et al. [76]; Tamamura, et al. [147]; Chen, et al. [198]; Liang, et al. [148]; Li, et al. [199]; Lee, et al. [200]; Liang, et al. [77]; Schmid, et al. [201]; Cabioglu, et al. [202]; Shim, et al. [203]; Liang, et al. [78]; Hao, et al. [92]
Esophageal cancer	Gockel, et al. [204]; Kaifi, et al. [205]; Koishi, et al. [206]; Sasaki, et al. [207]
Gastrointestinal Cancer	Ottaiano, et al. [97]; Tachibana, et al. [46]; Zeelenberg, et al. [95]; Kim, et al. [208]
Gynecological cancer	Kodama, et al. [209]; Jiang, et al. [210]; Pils, et al. [211]; Porcile, et al. [212]
Head and neck cancer	Samara, et al. [213]; Yoon, et al. [90]
Hepatocellular carcinoma	Begum, et al. [214]; Schimanski, et al. [215]; Shibuta, et al. [216]
Leukemia & Lymphoma	Barretina, et al. [217]; Burger, et al. [218]; Dao-Ung, et al. [219]; Fierro, et al. [220]; Ghobrial, et al. [221]; Voermans, et al. [62]; Ishibe, et al. [94]; Jin, et al. [222]; Juarez, et al. [223]; Konoplev, et al. [224]; Mohle, et al. [225]; Monaco, et al. [226]; Scupoli, et al. [227]; Spoo, et al. [228]; Tavor, et al. [229]; Wu, et al. [230]; Bertolini, et al. [231]; Chan, et al. [232]; Piovan, et al. [233]
Lung cancer	Kijima, et al. [133]; Spano, et al. [234]; Hartmann, et al. [135]; Burger, et al. [134]; Phillips, et al. [235]
Melanoma	Robledo, et al. [125]; Scala, et al. [126]; Murakami, et al. [127]; Takenaga, et al. [128]; Scala, et al. [129]; Longo-Imedio, et al. [130]
Multiple myeloma	Alsayed, et al. [236]; Moller, et al. [237]
Pancreatic cancer	Koshiba, et al. [151]; Mori, et al. [152]; Marchesi, et al. [238]; Hermann, et al. [104]
Prostate cancer	Taichman, et al. [239]; Darash-Yahana, et al. [240]; Sun, et al. [241]; Akashi, et al. [242]; Chinni, et al. [243]; Hart, et al. [244]; Mochizuki, et al. [245]; Wang, et al. [251246]
Renal carcinoma	Jones, et al. [247]; Pan, et al. [248]; Reckamp, et al. [249]; Staller, et al. [250]; Struckmann, et al. [251]
Sarcoma	Libura, et al. [252]; Laverdiere, et al. [253]; Oda, et al. [254]
Thyroid cancer	Hwang, et al. [255]; De Falco, et al. [256]