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Targeting Chemokine Receptor CXCR4 for Treatment of HIV-1 Infection, Tumor Progression, and Metastasis

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Abstract

The chemokine receptor CXCR4 is required for the entry of human immunodeficiency virus type 1 (HIV-1) into target cells and for the development and dissemination of various types of cancers, including gastrointestinal, cutaneous, head and neck, pulmonary, gynecological, genitourinary, neurological, and hematological malignancies. The T-cell (T)-tropic HIV-1 strains use CXCR4 as the entry coreceptor; consequently, multiple CXCR4 antagonistic inhibitors have been developed for the treatment of acquired immune deficiency syndrome (AIDS). However, other potential applications of CXCR4 antagonists have become apparent since its discovery in 1996. In fact, increasing evidence demonstrates that epithelial and hematopoietic tumor cells exploit the interaction between CXCR4 and its natural ligand, stromal cell-derived factor (SDF)-1α, which normally regulates leukocyte migration. The CXCR4 and/or SDF-1α expression patterns in tumor cells also determine the sites of metastatic spread. In addition, the activation of CXCR4 by SDF-1α promotes invasion and proliferation of tumor cells, enhances tumor-associated neoangiogenesis, and assists in the degradation of the extracellular matrix and basement membrane. As such, the evaluation of CXCR4 and/or SDF-1α expression levels has a significant prognostic value in various types of malignancies. Several therapeutic challenges remain to be overcome before the use of CXCR4 inhibitors can be translated into clinical practice, but promising preclinical data demonstrate that CXCR4 antagonists can mobilize tumor cells from their protective microenvironments, interfere with their metastatic and tumorigenic potentials, and/or make tumor cells more susceptible to chemotherapy.

Keywords

AIDS; CXCR4; HIV-1; SDF-1α; Tumor; vMIP-II

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INTRODUCTION: PHYSIOLOGICAL AND PATHOLOGIC FUNCTIONS OF CXCR4 AND SDF-1α

CXCR4 is one of the best studied chemokine receptors, as it serves as an important drug target for multiple human diseases, including HIV-1 infection and various types of malignancies (Fig. **1**) [1, 2]. CXCR4 belongs to the superfamily of G-protein-coupled receptors (GPCRs) that possess seven transmembrane (TM) domains. The natural chemokine ligand of CXCR4 is SDF-1α (also known as CXCL12), which activates CXCR4 via G-proteins (Table **1**) [3-6]. SDF-1α can also interact with another chemokine receptor, CXCR7, but this interaction does not activate signaling pathways typical of G-proteins [6]. The CXCR4–SDF-1α pathway plays many essential roles in the development of immune, nervous, vascular, and hematopoietic systems, and an important role has recently been identified in tissue regeneration [6-9]. The fact that knockout mice lacking either CXCR4 or SDF-1α die prenatally with multiple neurological, cardiac/vascular, and hematopoietic defects further demonstrates the physiological importance of CXCR4/SDF-1α [7, 8, 10]. In fact, CXCR4 is constitutively and widely expressed by numerous stem cell types, including liver oval, neural, hematopoietic, retinal pigment epithelial, endothelial, and embryonic stem cells, as well as skeletal muscle satellite cells and primordial germ cells [6]. SDF-1α is also widely expressed in multiple organs, including colon, liver, brain, lungs, heart, kidneys, and spleen [6].

Since its discovery in 1996, CXCR4 has become well known as an important coreceptor for HIV-1 infection. A fusion process between HIV-1 and target cells requires HIV-1 envelope glycoprotein, gp120, to first interact with the main receptor of the target cell, CD4, followed by its interaction with either CXCR4 or CCR5 [11-14]. HIV-1 initially uses CCR5 as the entry coreceptor to enter the target cells, and this strain is known as the macrophage (M)-tropic virus [12-14]. However, as the disease progresses, HIV-1 switches its coreceptor usage from CCR5 to CXCR4, and this T-cell (T)-tropic virus causes greater CD4-postive T-cell depletion and faster disease progression [15-17]. Natural chemokines of CXCR4 or CCR5 can directly inhibit HIV-1 infection at the entry level [18, 19] and/or internalize the coreceptors required for HIV-1 infection [20, 21].

In addition to its main role as a HIV-1 coreceptor, CXCR4 is now recognized as the chemokine receptor most widely expressed by various types of malignant tumors (Fig. **1**). Indeed, it plays important roles in the development and dissemination of more than 75% of all cancers, including gastrointestinal (esophageal, gastric, pancreatic, hepatocellular, and colorectal), cutaneous, head and neck, pulmonary, gynecological (breast and ovarian), genitourinary (renal and prostate), neurological, and hematological malignancies [6, 22, 23]. SDF-1α expression level is also the highest in common metastatic sites, including lungs, lymph nodes, and liver. This indicates that CXCR4-expressing tumor cells metastasize to SDF-1α-secreting distant organs via the CXCR4–SDF-1α pathway [22]. Therefore, the evaluation of CXCR4/SDF-1α expression level may have a significant prognostic value in various types of malignancies, because the high expression of CXCR4 or SDF-1α has been shown to predict poor survival outcomes in colon [24], pancreatic [25], prostate [26], breast [27], ovarian [28], and lung cancer patients [29]. Furthermore, blocking the interaction

between CXCR4 and SDF-1α is supported by the available data as an effective therapeutic strategy that would interfere with the metastatic and tumorigenic potentials of diverse types of malignancies.

One important mechanism that drives the metastatic behavior of tumor cells is hypoxia [1]. Decreased oxygen in the tumor microenvironment increases the concentration of hypoxia-inducible factor-1 (HIF-1), which subsequently upregulates the expression of CXCR4 in many tumor cells [22, 30]. SDF-1α activates CXCR4, and this in turn mediates invasion and proliferation of tumor cells, enhances tumor-associated neoangiogenesis, and assists in the degradation of the extracellular matrix and basement membrane [6, 22]. The important implication of this observation is that although a particular anti-cancer therapy might remove the primary tumor, it can potentially increase the metastatic potential of the surviving tumor cells by promoting a hypoxic environment and increasing CXCR4 expression. Hence, disrupting a particular disease function of CXCR4 or preventing the upregulation of CXCR4 in cancer cells may be impetrative for effective cancer treatment.

Several studies indicate that tumors are composed of different cell subtypes that contribute disproportionately to proliferation and invasion. The identification of so called “cancer stem cells” (CSCs) has led to the viewpoint that cancer therapies should be targeted towards these progenitor cells rather than the entire tumor burden. These CSCs are similar to normal stem cells in that they can self-renew, thereby recapitulating tumors in ectopic settings [31] and initiating tumor growth, therapy resistance, and tumor recurrence [32, 33]. In this regard, CXCR4 plays crucial roles in the maintenance, dissemination, and metastatic colonization of CSCs in various types of malignancies, including renal, prostate, colon, pancreatic, and lung cancers [6, 34].

In this review, we highlight the functions of CXCR4 and SDF-1α, as they pertain to HIV-1 infection, tumor progression, and metastasis, involving gastrointestinal, cutaneous, head and neck, pulmonary, gynecological, genitourinary, neurological, and hematological malignancies. The preclinical and clinical studies supporting the potential efficacy of CXCR4 inhibitors as the treatments of HIV-1 and cancer, and challenges that must be overcome before the translation of these inhibitors into the clinic are also discussed.

INHIBITION OF CXCR4 PREVENTS HIV-1 ENTRY

In 1996, CXCR4 was identified as one of the two essential coreceptors required for HIV-1 infection [11]. The feasibility of a CXCR4-based therapeutic approach for inhibiting HIV-1 infection is supported by the fact that CCR5 mutations confer individuals with resistance to HIV-1 infection [35, 36]. Several earlier CXCR4 antagonistic compounds, including AMD3100 and ALX40-4C (Table **1**), were developed by random screening work [37-42]. Both AMD3100 and ALX40-4C inhibit HIV-1 infection by directly blocking the interaction between CXCR4 and HIV-1 [40, 43-45]. Poor oral bioavailability of AMD3100 was overcome by developing derivatives with fewer basic amine groups, such as AMD3465 [46] and AMD070 [47] (Table **1**). The KRH-3955 [48, 49] and GSK812397 antagonists [50] were also found to have improved oral bioavailability and more potent antiviral activities than AMD3100 (Table **1**). Similarly, T22, T140, TC14012, and FC131 can inhibit HIV-1

entry via CXCR4 (Table **1**) [51-53], and smaller, yet more potent, anti-HIV peptide [54, 55] or nonpeptide compounds [56] have been developed more recently, based on the structure of T140. Furthermore, CGP64222, R3G, and NeoR were reported as potent CXCR4 antagonistic inhibitors (Table **1**) [57, 58].

Random screening has been supplemented by the use of natural chemokines, such as SDF-1α and viral macrophage inflammatory protein (vMIP)-II (Table **1**), as the design templates for synthesis and engineering of a group of short peptides or full-length synthetic chemokines [38, 39, 42, 59-65]. Unlike SDF-1α, vMIP-II binds to multiple chemokine receptors, including CXCR4 [66, 67], and the peptide derived from the first 1-21 residues of vMIP-II, designated as V1 (Table **1**), blocks both T- and dual-tropic HIV-1 viruses. Interestingly, the antiviral and binding activities were more potent for an all-D-amino acid analog of V1 peptide (also known as DV1) than for V1 peptide (Table **1**) [39]. Modification of only a small sequence of natural chemokines, especially the amino (N)-terminal domain, resulted in the development of a new group of synthetic chemokines called SMM (synthetically and modularly modified)-chemokines [68]. For instance, RCP168 can selectively inhibit CXCR4. It has more potent anti-HIV activity than is observed with SDF-1α but comparable potency to that of T-20 peptide, which is marketed under the trade name Fuzeon (Table **1**) [68-70]. Despite its strong binding and antiviral activities, RCP168 does not significantly interfere with SDF-1α signaling, which is important for maintaining the normal physiological functions of CXCR4 [71].

These advances in the development of new CXCR4 antagonistic inhibitors are still limited by the potential adverse outcomes arising from the use of these inhibitors. Blocking the interaction between CXCR4 and SDF-1α for HIV-1 therapy raises concerns, especially with the finding that CXCR4 [8, 10] or SDF-1α [7] knockout mice die prenatally with multiple neurological, cardiac/vascular, and hematopoietic defects [72]. As such, Sachpatzidis *et al.* reported the development of allosteric agonists, RSVM and ASLW (Table **1**), which can activate CXCR4 even in the presence of other CXCR4 antagonistic inhibitors or antibodies [42]. Allosteric modulators can bind to GPCRs at sites that differ from those of endogenous orthosteric agonists [73]. Allosteric agonists may be beneficial in therapeutic applications, as they could potentially allow retention of essential CXCR4 physiological functions.

Recently, the importance of CXCR4 dimerization in CXCR4 functions has been demonstrated by studies on the crystal structure of CXCR4 [74-77]. In this regard, the DV1 dimer (a synthetic bivalent ligand based on the DV1 monomer) showed more potent antiviral and binding activities when compared to the DV1 monomer (Table **1**) [78]. Tanaka *et al.* also synthesized a dimeric form of an FC131 analog (Table **1**), and bitopic ligands are currently being developed by combining orthosteric and allosteric pharmacophores in one ligand. Allosteric pharmacophores will target allosteric/therapeutic targets, whereas concurrent interaction with the orthosteric sites will ensure receptor activation and prevent undesired side effects [73]. For instance, pyrazole GPR109 receptor agonists recently provided the proof of concept; analogs of acifran selectively activate the Gi pathway that mediates the beneficial lipolytic effect, but not the β-arrestin pathway involved in the adverse side effect of cutaneous flushing [73, 79, 80]. These findings certainly represent an exciting opportunity for novel drug discovery that specifically targets therapeutically

relevant binding sites and/or signaling pathways of CXCR4, which plays an important role in HIV-1 infection, tumor progression, and metastasis. Fig. (**1**) shows a cartoon representation of orthosteric and allosteric modulators of CXCR4 and their therapeutic potentials for regulating physiological and pathological processes. Table **1** also summarizes representative CXCR4 modulators that are subcategorized into orthosteric, allosteric, cyclic, dimerized, or bivalent groups.

CXCR4 INHIBITION AGAINST GASTROINTESTINAL MALIGNANCIES

The importance of CXCR4 has been described in various types of gastrointestinal tumors, including esophageal, gastric, pancreatic, hepatocellular, and colorectal cancers [22]. A meta-analysis of a total of 1,055 esophageal cancer patients showed that CXCR4 overexpression increases the risk of bone marrow and lymph node metastases and therefore indicates worse survival outcomes [81]. Patients with CXCR4-positive tumors have a median survival of 20 months, whereas the median survival of patients with CXCR4-negative tumors is 76 months [82]. Although medical options are limited for patients with esophageal carcinoma, recent data suggest that CXCR4 antagonists might be attractive therapeutic candidates for treatment of esophageal cancer. For instance, Drenckhan *et al.* reported that CTCE-9908 (Table **1**) targets CXCR4 and prevents both tumor growth and metastases to liver, lungs, and lymph nodes in an orthotopic model of esophageal carcinoma [83]. This finding was further supported by a report that downregulation of CXCR4 expression by small interfering RNA (siRNA) can increase apoptosis and inhibit esophageal tumor growth [84].

Similarly, the prognosis of advanced gastric cancer remains poor, and its therapy relies largely on cytotoxic chemotherapy [85]. Strong CXCR4 expression in gastric cancer is significantly associated with cancer cell migration, lymph node metastases, higher tumor stages, and reduced 5-year survival rate [86]. Eighty-five percent of CXCR4-expressing gastric tumors develop carcinomatosis in the peritoneum, a major cause of gastric carcinoma-related death [87]. A high level of SDF-1α is found in peritoneal mesothelial cells, which promotes the migration of gastric cancer cells that express CXCR4 to the peritoneum. The CXCR4 mRNA level in gastric cancer tissues also correlates with docetaxel sensitivity, and it is significantly higher in resistant specimens [88]. Thus, identifying novel therapeutic approaches to prevent gastric cancer progression and to overcome treatment resistance is an important goal. In this regard, several pre-clinical studies demonstrated that anti-CXCR4 monoclonal antibodies and AMD3100 have anti-tumor activity by significantly suppressing tumor cell migration, proliferation, and survival [85]. Furthermore, AMD3100 can reduce ascitic fluid formation [87] and enhance *in vitro* docetaxel cytotoxicity [88].

Pancreatic cancer, one of the most lethal human malignancies, is also associated with the high expression level of CXCR4 [89]. Stromal cells and distant organs release SDF-1α, which in turn enhances proliferation, invasion, and metastasis of pancreatic cancer cells, and upregulates matrix-degrading enzymes [89]. Gemcitabine-treated pancreatic cancer cells develop high resistance to chemotherapy in the presence of SDF-1α, indicating that pancreatic cancer cells become more drug resistant upon the activation of CXCR4 by

SDF-1α [90]. Interestingly, the pharmacological intervention by AMD3100 can effectively inhibit all these processes. Furthermore, the metastatic potential of CXCR4-expressing pancreatic CSCs can be abrogated by CXCR4 inhibition without affecting their tumorigenic capability [91]. As such, these findings indicate that the modulation of the CXCR4–SDF-1α pathway may have an important role in inhibiting aggressive pancreatic tumors.

In the case of hepatocellular carcinoma (HCC), accumulating evidence indicates that the CXCR4–SDF-1α signaling cascade mediates tumor growth, invasion, and metastasis, which is responsible for the majority of deaths in patients with HCC [92]. In fact, CXCR4 expression is significantly correlated with advanced primary tumor, lymphatic metastasis, distant dissemination, and poor survival rate [93]. The high expression level of CXCR4 also correlates with the activation of the transforming growth factor (TGF)-β pathway, a less differentiated phenotype, and a cirrhotic background [94]. Furthermore, a HCC mouse model demonstrated that SDF-1α-induced CXCR4 activation promotes the secretion of matrix metalloproteinases (MMPs), which is associated with increased metastatic potential [95]. However, antibody neutralization of either CXCR4 or SDF-1α significantly reduces the secretion of MMPs and lymph node metastasis. More recently, an anthraquinone derivative, emodin, was found to downregulate the expression of CXCR4, thus suppressing HCC invasion [92]. Emodin can also significantly suppress lung metastasis in a HCC mouse model.

CXCR4 expression is also associated with recurrence, metastasis, and survival in patients with colorectal cancer [96]. Gao's analysis of 720 cases of colorectal cancer demonstrated that CXCR4 expression is elevated in colorectal cancer tissues. In addition, lymph node metastasis, higher histological grade and tumor node metastasis (TNM) stage, and liver metastasis are correlated with CXCR4 expression, further indicating that CXCR4 may serve as an important biomarker for both liver metastasis and survival in colorectal cancer patients [96]. Another study showed greater expression of CXCR4 in metastatic foci (such as liver and lymph nodes) than in primary tumors. Colorectal cancer cell lines in which the expression of CXCR4 was reduced via microRNA demonstrated significantly reduced metastases to liver, lymph nodes, and lungs [97]. The pharmacologic inhibition of the CXCR4–SDF-1α interaction by AMD3100 also significantly reduces CXCR4-dependent migration of colorectal cancer cells [98]. Furthermore, a recent demonstration confirmed that CXCR4 can be targeted by microRNA (miR)-126, a tumor suppressor in colorectal cancer that inhibits the Ser/Thr kinase AKT and extracellular signal-related kinase 1/2 (ERK1/2) signaling pathways. Liu *et al.* reported that miR-126 overexpression negatively regulates CXCR4, inhibits tumor cell proliferation, migration, and invasion, and induces cell cycle arrest in the G0/G1 phase of colorectal cancer cells [99].

CXCR4 INHIBITION AGAINST CUTANEOUS MALIGNANCIES

The CXCR4 expression by malignant melanoma is predictive of metastasis, increased tumor thickness, ulceration, and poor survival rate [100]. Scala *et al.* demonstrated that CXCR4 expression is associated with a poor prognosis in malignant melanoma patients, with an overall survival time of 35 months [101]. Another study indicated that CXCR4 expression was one of the independent prognostic factors in these patients [101]. Furthermore, CXCR4

plays an important role in the initial implantation of melanoma cells into the lungs, while membrane-bound metalloproteinase MT1-MMP accumulates intracellularly via the Rac-ERK1/2 pathway and mediates invasion and metastasis of the tumor cells [102]. AMD3100 can inhibit the spontaneous and SDF-1α-induced proliferation of melanoma cell lines [103]. More recently, a covalently locked, dimeric variant of SDF-1α, CXCL122 (Table **1**), was shown to inhibit implantation of lung metastasis of melanoma cells more effectively than AMD3100, and also to block the growth of established metastatic melanoma in the lungs [104].

CXCR4 overexpression is also significantly associated with tumor size and invasive/infiltrating type in basal cell carcinoma (BCC) [105]. BCC highly expresses transforming growth factor (TGF)-β1, which induces upregulation of CXCR4 through the phosphorylation of the ERK1/2-ETS-1 (v-ets avian erythroblastosis virus E26 oncogene homolog 1) pathway [106]. Chu *et al.* demonstrated that BCC with higher CXCR4 expression has concomitantly higher microvessel density, and that SDF-1α induces angiogenic activity by upregulating several genes associated with angiogenesis, including interleukin (IL)-6, bone morphogenetic protein (BMP)-6, and cyclooxygenase 2 (COX)-2 [107]. Consistent with the important role of CXCR4 in the pathogenesis of BCC, neutralizing antibodies and the CXCR4-blocking peptide, T22, can both negate the increased proliferation and resistance to apoptosis in BCC following treatment with SDF-1α [108]. Furthermore, transplants of CXCR4-BCC into nude mice showed significant tumor progression, whereas the CXCR4 inhibitor T22 promoted tumor regression.

CXCR4 INHIBITION AGAINST HEAD AND NECK MALIGNANCIES

Approximately 10% of all human cancers are caused by head and neck malignancies [23]. The most common type is head and neck squamous cell carcinoma (HNSCC), representing greater than 90% of all head and neck cancers, and up to a quarter of patients develop metastasis with a poor survival outcome [23, 109]. In the hypoxic environments of the head and neck, the CXCR4–SDF-1α system is significantly upregulated via HIF-1, and is known to promote tumor aggressiveness and metastatic dissemination [23, 110]. In fact, CXCR4-positive patients have a 5-year survival rate of 39.1% versus 71.4% for CXCR4-negative patients [111]. Several groups also have reported a significant association between lymph node metastasis and the expression of CXCR4 in HNSCC [111, 112]. For instance, Uchida *et al.* demonstrated that lymph node metastasis in HNSCC is controlled by SDF-1α-induced CXCR4 activation via ERK1/2 or AKT/protein kinase B (PKB) pathway, as U0126 (mitogen-activated protein kinase (MEK)/ERK kinase inhibitor) or wortmannin (phosphatidylinositol 3 kinase (PI3K) inhibitor) can inhibit lymph node metastasis [113]. Another study on nude mice injected with B88-SDF-1 (SDF-1α expression into the B88 cell line) reported the development of an increased number of metastatic lymph nodes, more aggressive metastatic foci in the lymph nodes, and dramatic metastasis to the lungs [111]. AMD3100 significantly inhibited the lung metastasis, ameliorated body weight loss, and improved the survival rate of mice. Blocking CXCR4 via an siRNA strategy can also induce anti-tumor effects [114, 115]. Furthermore, TN14003, a small synthetic peptide antagonist of CXCR4, can reduce tumor growth, microvessel density, and lung metastasis in tumor-bearing nude mice (Table **1**) [116].

CXCR4 INHIBITION AGAINST PULMONARY MALIGNANCIES

Pulmonary malignancy is the second most frequent human tumor, with a higher mortality rate than the next four common cancers combined (colon, breast, pancreatic, and prostrate cancers) [117]. In fact, the reported overall survival rate within 5 years is a mere 15% [117, 118]. Two types of lung cancers are recognized: non-small cell (NSCLC, 80%) and small cell lung cancers (SCLC, 20%) [117]. All major subtypes of NSCLC express CXCR4, and tumors with higher CXCR4 expression are more prone to metastasis than are low-expression tumors [119]. Similarly, SCLC not only expresses CXCR4 ubiquitously, but also responds to SDF-1α with an increase in cell proliferation, adhesion, and motility [120]. SCLC preferentially metastasizes to the bone marrow, whereas NSCLC tends to metastasize to bones [121].

Stage IV NSCLC patients with high expression of CXCR4 also have an extremely poor median survival time of only 2.7 months (compared to 5.6 months for low CXCR4-expressing patients) [122]. The overexpression of CXCR4 seems to have a greater impact on the clinical outcome of the female population, which has a median overall survival of 1.6 months. Furthermore, recent reports indicate that CXCR4 is expressed by CSCs in NSCLC, and that inhibition and/or siRNA targeting of CXCR4 and of the downstream action of signal transducer and activator of transcription 3 (STAT3) significantly suppress the self-renewal and chemoresistant capacity of various NSCLC cell lines [123]. Taken together, these studies certainly support the notion that CXCR4/SDF-1α plays a pro-malignant role in NSCLC disease progression.

These results also point to an urgent need for novel CXCR4-targeted therapeutics against NSCLC. In fact, the *in vitro* inhibition of the CXCR4–SDF-1α interaction via CXCR4-specific antibodies was shown to inhibit NSCLC metastasis [119]. Inoculation of nude mice with lung cancer cells with low CXCR4 expression also resulted in a 0- to 2-fold decrease in lung metastatic foci compared to inoculation with cells with high expression of CXCR4. In addition, AMD3100 and BKT140 (Table **1**), which specifically block CXCR4, attenuate NSCLC tumor growth, suppress self-renewal capacity, and augment the effects of chemotherapy and radiotherapy [124, 125]. Thus, the CXCR4–SDF-1α axis offers an exciting new target for the development of novel anti-cancer chemokine-based therapeutics.

In SCLC, SDF-1α activates CXCR4 and tumor-associated integrin. This activation increases the adhesion between SCLC cells to collagen and fibronectin within the tumor microenvironment [1, 126]. As such, relapse and residual disease are common in SCLC, as tumor cells adhere to the bone marrow stromal cells and/or extracellular matrix proteins via integrins and are therefore protected from chemotherapy. Indeed, CXCR4 inhibitors, such as T140, can prevent the adhesion of tumor cells to extracellular membranes, thereby increasing the sensitivity of SCLC to chemotherapy [126].

CXCR4 INHIBITION AGAINST FEMALE REPRODUCTIVE MALIGNANCIES

In contrast to normal breast tissue, both primary and metastatic breast tumors highly express CXCR4 [127]. Hung *et al.* divided cancer patients into low-level and high-level CXCR4 expression groups using immunohistochemical staining, and demonstrated that the high-

level CXCR4 expression group had a higher incidence of distant metastasis, especially bone metastasis, during the first year (10.3 % versus 1.1 %) and shorter event-free survival (17.43 months versus 27.5 months) [128]. The CXCR4–SDF-1α pathway mediates the formation of pseudopodia by actin polymerization, which increases the chemotactic and metastatic potentials of breast cancer cells [127]. Yan *et al.* also observed that abnormal activation of the human epithelial growth factor receptor (HER)-2 in breast cancer cells upregulates CXCR4 expression and mediates tumor invasion and lung metastasis via PI3K/AKT/mammalian targets of the rapamycin (mTOR) pathway [129]. Given the importance of CXCR4 in breast carcinogenesis, the observation that a neutralizing antibody against CXCR4 prevents breast cancer metastasis to lungs and lymph nodes is not surprising [127]. T140 derivatives and CTCE-9908 can also effectively reduce metastasis as well as primary tumor growth [130, 131]. The specific CXCR4 inhibitor AMD3465 was recently shown to trigger a reduction in breast cancer cell invasiveness and metastases to the lungs and liver through the modulation of oncogenic signaling that includes the STAT3 pathway [132]. Furthermore, siRNA duplexes can inhibit invasion and metastasis of breast cancer cells in an animal model by preventing CXCR4 expression [133].

Similarly, the expression of CXCR4 is an independent prognostic marker of ovarian carcinoma, a common gynecological malignancy [134]. The multivariate analysis by Jiang *et al.* indicated that CXCR4 expression is higher in recurrent and refractory ovarian cancers than in non-recurrent cancers (81% versus 28%) [134]. CXCR4 expression was predictive of significantly reduced overall survival after a median follow-up of 37 months, and the intensity of SDF-1α staining correlated with ascites. CXCR4 expression is also shown to be responsible for SDF-1α-induced ovarian cancer cell invasion and extracellular matrix degradation through αvβ6 integrin-mediated urokinase-type plasminogen activator (uPA) expression via the p38 MAPK and PI3K/AKT pathways [135]. This process can be prevented with the CXCR4 inhibitor AMD3100. Significantly lower cisplatin-based chemosensitivity, a poorer progression-free survival, and a lower overall survival were recently found to be associated with high CXCR4 expression. This suggests that CXCR4 is one of the key molecules responsible for cisplatin-based chemoresistance in epithelial ovarian cancer [136]. In fact, knockdown of CXCR4 by siRNA suppresses *in vitro* cell proliferation, results in G1/S arrest, and increases apoptosis and chemosensitivity in both cisplatin-sensitive and cisplatin-resistant cells [136].

CXCR4 INHIBITION AGAINST GENITOURINARY MALIGNANCIES

Renal cell carcinoma (RCC) expresses a high level of CXCR4 compared to normal kidney tissues [137]. Strong CXCR4 expression in RCC is significantly associated with advanced T-status, tumor dedifferentiation, and poor overall and recurrence-free survival [138, 139]. Pan *et al.* used severe combined immunodeficiency (SCID) mouse models to demonstrate that the high expression of CXCR4 in RCC is predictive of increased metastasis, and that enhanced CXCR4 expression is mediated by HIF-1 [30, 140]. The neutralization of SDF-1α in SCID mice abrogates RCC metastasis to SDF-1α-expressing distant organs. Recently, CSCs in RCC were found to express CXCR4 [141]. These CXCR4-positive CSCs exhibit greater tumor sphere formation and *in vivo* growth potential, and they are more resistant to tyrosine kinase inhibitors, such as sunitinib, sorafenib, and pazopanib. In fact, AMD3100 or

siRNA can downregulate CXCR4 expression and increase the sensitivity of CSCs to tyrosine kinase inhibitors, thereby reducing the capability of CSCs to modulate tumor growth [141].

Sun *et al.* used high density microarrays to demonstrate that CXCR4 expression is also significantly elevated in localized and metastatic prostate cancers [142]. Bone metastatic foci of prostate cancer express higher level of CXCR4 compared to primary tumors and other metastatic lesions [143]. Loss of PTEN (phosphatase and tensin homolog) and subsequent activation of AKT increase the expression of CXCR4 and SDF-1α, as well as tumor cell proliferation and cell cycle progression [144]. In this study, AKT inhibition was shown to reverse CXCR4 expression and cellular invasion in prostate cancers. Furthermore, in the human prostate cancer PC-3 tumor xenograft model, AMD3100 significantly inhibited SDF-1α-induced CXCR4/AKT signal transduction and tumor growth, while AMD3100-treated PC-3 tumors showed lower *in vivo* levels of microvessel formation, proliferative index (as demonstrated by Ki-67), and anti-apoptotic protein Bcl-2 (B-cell lymphoma 2) compared to control tumors [145]. In addition, AMD3100 can chemosensitize prostate cancer cells to docetaxel [143]. A subcutaneous xenograft mouse model was used to show that combination therapy of AMD3100 and docetaxel has a more potent antitumor effect than does mono-chemotherapy.

CXCR4 INHIBITION AGAINST NEUROLOGICAL MALIGNANCIES

The most common intracranial tumors found in adults are gliomas, and the most aggressive subtype is glioblastoma multiforme (GBM) [34, 146]. The highly infiltrative nature of GBM, with numerous microscopic satellites that often migrate significant distances from the primary tumor, has prevented the currently available surgical techniques and adjuvant therapies from significantly improving the overall survival rate of patients with GBM [34]. However, recent research showed that CXCR4 is overexpressed in primary GBM progenitor cells, and that the administration of SDF-1α stimulates a significant proliferation of CSCs, but not of differentiated tumor cells [147]. This indicates that the CXCR4–SDF-1α pathway is a potent regulator of glioma stem cell proliferation. The evaluation of CXCR4 expression level may in fact have a significant clinical prognostic value in glioma patients. Brian *et al.* showed that the high expression level of CXCR4 is associated with increased glioma tumor grade and is predictive of poorer prognosis after surgery [148]. The inhibition of CXCR4 further reduces the metastasis of these invasive neoplastic glial cells [149].

A significant blood supply is needed for tumor growth and progression and is maintained by the release of HIF-1 from gliomas in the setting of an increasingly hypoxic environment. This then leads to the activation of a number of genes that function to increase oxygen availability to tumor cells [34]. In this regard, CXCR4 was identified as an activator of HIF-1, and its expression is significantly upregulated by vascular endothelial growth factor (VEGF) in both glioma and endothelial cells, demonstrating the importance of CXCR4 in glioma angiogenesis [150]. Treatment with AMD 3100 can significantly inhibit the mobilization of glioma cells in oxygen-deprived conditions. GBM recurrence can also be prevented by AMD3100 and neutralizing antibodies through inhibition of the development of functional tumor vasculogenesis [151]. Rubin *et al.* reported that AMD3100 can increase

the apoptosis of GBM, thereby decreasing its growth potential [152]. Redjal *et al.* showed that GBM treated with a combination therapy involving 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and AMD3100 results in synergistic antitumor efficacy both *in vitro* and *in vivo* [153]. Knockdown of CXCR4 via RNA interference or AMD3100 was recently reported to reduce the amount of *in vitro* VEGF produced by glioma CSCs and to attenuate the *in vivo* tumor angiogenesis and growth [154].

CXCR4 INHIBITION AGAINST HEMATOLOGICAL MALIGNANCIES

The CXCR4–SDF-1α pathway mediates the interaction between stromal and leukemic cells. Both acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL) can spontaneously infiltrate the bone marrow and avoid chemotherapy-induced apoptosis by activating the CXCR4–SDF-1α pathway [155-157], thereby acquiring necessary mutations required for chemotherapy resistance. In this regard, RCP168 has been shown to inhibit stromal–leukemia cell interaction via CXCR4 and to release CLL and AML cells from the bone marrow microenvironment into peripheral blood, where they can be targeted by chemotherapy [70]. Burger *et al.* also showed that CXCR4-specific antagonists (T140 or its analogs) can effectively antagonize the migration of CLL cells induced by SDF-1α, and enhance apoptosis of leukemic cells when used in combination with fludarabine [121]. In addition, AMD3100 [158] and AMD3465 [70] achieved similar outcomes, further indicating that the CXCR4–SDF-1α pathway may indeed represent an effective drug target for increasing the number of leukemic cells available in peripheral blood that can be targeted by chemotherapy.

Hematopoietic stem cell (HSC) transplants are most often performed in patients with hematological malignancies, such as multiple myeloma and leukemia. Adult bone marrow contains trilineage hematopoietic elements (i.e., myeloid, erythroid, and megakaryocytic cells), and it is the primary source of SDF-1α [159]. Chemotactic responsiveness of HSCs is restricted to SDF-1α, and this selectivity for SDF-1α is necessary for retention, growth, and differentiation of HSCs in the bone marrow [1]. Both HSCs and hematopoietic progenitor cells (HPCs) can be induced to exit the bone marrow [160, 161] and collected in peripheral blood for hematopoietic stem cell transplantation in patients undergoing high-dose chemotherapy for their hematological malignancies. Currently, granulocyte colony-stimulating factor (GCSF) is used most often in clinical practice to increase the number of HSCs in blood for collection for transplantation, although this treatment is associated with unwanted side effects and requires multiple doses [162]. In this regard, several studies have shown that CXCR4-expressing HSCs and HPCs are retained within the bone marrow that expresses SDF-1α [163-165]. Indeed, AMD3100 [166] or T140 [167] can mobilize HSCs by blocking CXCR4, and for this reason, AMD3100 (Plerixafor) was approved in 2008 for the treatment of patients with lymphoma and multiple myeloma to increase the number of HSCs available for transplantation. Similarly, a lipopeptide pepducin, ATI-2341, can inhibit the function of CXCR4 and increase the mobilization of HSCs and HPCs (Table **1**) [168]. HSC mobilization can also be effectively induced by inhibitory CXCR4 nanobodies and AMD3100 [169].

CONCLUSION

Tremendous progress has been made in drug discovery research targeting CXCR4 since the first report in 1996 that CXCR4 is one of the two essential coreceptors for HIV-1 infection [11]. Indeed, the research focus has expanded to include multiple types of cancers, including gastrointestinal, cutaneous, head and neck, pulmonary, gynecological, genitourinary, neurological, and hematological malignancies. Although the collective evidence supports the potential efficacy of CXCR4 inhibitors as therapies for HIV-1 and cancer treatments, important challenges remain before CXCR4 inhibitors will be sanctioned for clinical use, due to the ubiquitous expression of CXCR4 in normal tissues and the functional importance of the CXCR4–SDF-1α interaction, as discussed in this review. One of the major concerns regarding the use of CXCR4 inhibitors as HSC mobilizers is that these may expose not only leukemic cells but also normal hematopoietic cells to cytotoxic chemotherapy. These limitations demonstrate that therapeutic strategies should be aimed at selective disruption of a particular disease function of CXCR4 without compromising its normal functions. In fact, although the use of AMD3100 as a mobilizer of HSCs in patients with non-Hodgkin's lymphoma and multiple myeloma has shown minimal side effects, its use was discontinued in a clinical study for HIV-1 treatment due to cardiac toxicity [6]. In this regard, several studies have shown that CXCR4 may have two distinct binding sites for HIV-1 gp120 and SDF-1α [170], and that SMM-chemokines, such as RCP168, can selectively disrupt HIV-1 entry without compromising the normal SDF-1α binding and signaling activities [71].

Similarly, the selective targeting of tumor-specific CXCR4–SDF-1α pathways involved in tumor progression and metastasis must not inhibit global CXCR4 signaling. Bitopic ligands that can selectively target therapeutically relevant binding sites and/or signaling pathways of CXCR4, thereby reducing unwanted side effects, represent exciting candidates for novel anti-cancer drug discovery. In summary, most studies on the CXCR4–SDF-1α axis and its inhibition for the treatment of cancers are still in their infancy, but pre-clinical data indicate some encouraging results. This has opened up the possibility that CXCR4 inhibitors may have therapeutic benefits, especially when used in combination with existing treatment strategies.

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LIST OF ABBREVIATIONS

CXCR4	CXC chemokine receptor 4
GPCR	G-protein-coupled receptor

SDF-1α	Stromal cell-derived factor-1α
vMIP-II	Viral macrophage inflammatory protein-II
HIV	Human immunodeficiency virus
AIDS	Acquired immune deficiency syndrome
HIF-1	Hypoxia-inducible factor-1
CSC	Cancer stem cell
HCC	Hepatocellular carcinoma
BCC	Basal cell carcinoma
HNSCC	Head and neck squamous cell carcinoma
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
RCC	Renal cell carcinoma
GBM	Glioblastoma multiforme
CLL	Chronic lymphocytic leukemia
AML	Acute myelogenous leukemia
HSC	Hematopoietic stem cell
HPC	Hematopoietic progenitor cell
G-CSF	Granulocyte colony-stimulating factor

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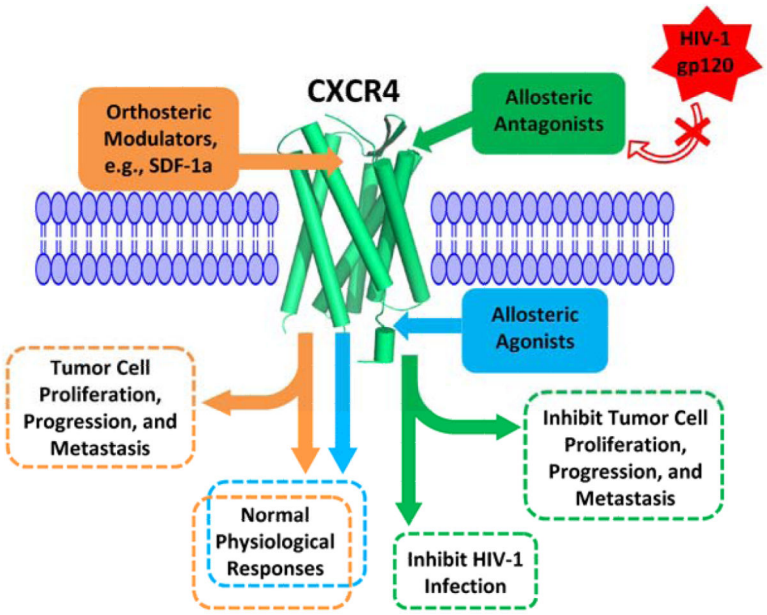
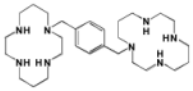
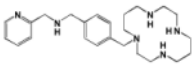
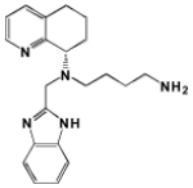
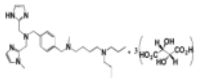
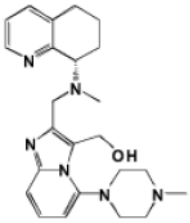


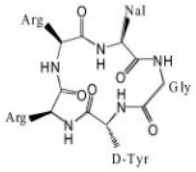
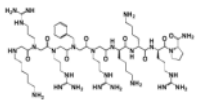
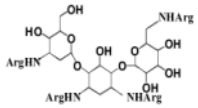
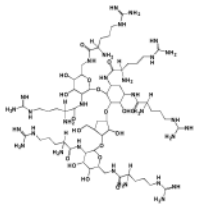
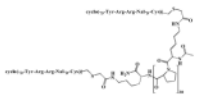
Fig. (1).

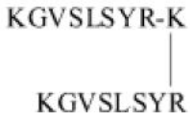
Schematic representation of CXCR4 with updated orthosteric/allosteric modulators and their biological effects.

Table 1

Representative CXCR4 Antagonists and Agonists.

Name	Chemical Structure	Binding Activity (IC_{50}, nM)[b]		Migration Activity	Calcium Mobilization	Anti-HIV Activity (IC_{50}, nM)[c]	Type of Modulator and References
		SDF-1α	12G5				
SDF-1α	KPVSLSYRCPCRFFESHVARANVK HLKILNTPNCALQIVARLKNNNRQ VCIDPKLKWIQEYLEKALNK	4	20	+[f]	+	730	Linear Peptide Modulator [171-175]
ALX40-4C	Ac-NH-RRRRRRRRR-$CONH_2$	ND[e]	3,200	ND	–[g]	3	Linear Peptide Modulator [37, 43, 173]
AMD3100		33	37.5	–	–	12.4	Orthosteric Modulator [46, 176, 177]
AMD3465		18	0.75	–	–	12.3	Orthosteric Modulator [46, 177]
AMD070		13	ND	ND	ND	2	Orthosteric Modulator [47, 178]
KRH-3955		0.61	2.8	ND	–	0.99	Orthosteric Modulator [48]
GSK812397		0.87	ND	–	–	4.60	Orthosteric Modulator [50]
T22		ND	48	ND	–	5.1	Cyclic/Orthosteric Modulator [51, 173]
T140	H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-$NH2^a$	2.4	2.5	–	–	0.43	Cyclic/Orthosteric Modulator [121, 130, 173, 179]
TC14012	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-D-Cit-Pro-Tyr-Arg-Cit-Cys-Arg-$NH2^a$	2.9	ND	–	ND	37	Cyclic/Orthosteric Modulator [130, 179]

Name	Chemical Structure	Binding Activity (IC_{50}, nM)[b]		Migration Activity	Calcium Mobilization	Anti-HIV Activity (IC_{50}, nM)[c]	Type of Modulator and References
		SDF-1α	12G5				
FC131		4	ND	ND	ND	14	Cyclic/Orthosteric Modulator [54, 55, 180-182]
CGP64222		ND	ND	ND	–	1,386 1.8 (μg/ml)	Orthosteric Modulator [57, 58]
R3G		ND	7,700	ND	–	15,000	Orthosteric Modulator [183]
NeoR		ND	ND	ND	ND	800	Orthosteric Modulator [184, 185]
vMIP-II	LGASWHRPDKCCLGYQKRPLPQVL LSSWYPTSQLCSKPGVIFLTKRGR QVCADKSKDWVKKLMQQLPVTAR	14.8	3.0	ND	–	ND	Linear Peptide Modulator [38, 66, 67]
V1	LGASWHRPDKCCLGTQKRPLP	190	640	–	–	ND	Linear Peptide Modulator [38, 39, 62]
DV1	*LGASWHRPDKCCLGYQKRPLP* [d]	13	32	–	–	12,100	Linear Peptide Modulator [39, 78]
RCP168	*LGASWHRPDK*CCLGYQKRPLPQVL LSSWYPTSQLCSKPGVIFLTKRGRQ VCADKSKDWVKKLMQQLPVTAR	5	5	–	–	50	Dimerized/Bivalent/ Orthosteric Modulator [68-70]
RSVM	RSVMLSYRCPCRFFESH	ND	ND	+	+	ND	Allosteric Modulator [42, 186]
ASLW	ASLWLSYRCPCRFFESH	ND	ND	+	+	ND	Allosteric Modulator [42, 186]
DV1 Dimer	*LGASWHRPDKCA-LGYQKRPLP* | *LGASWHRPDKCA-LGYQKRPLP*	ND	3	ND	–	4,400	Dimerized/Bivalent/ Orthosteric Modulator [78]
FC131 Analog		9.9	ND	ND	ND	ND	Dimerized/Bivalent/ Orthosteric Modulator [187]

Name	Chemical Structure	Binding Activity (IC_{50}, nM)[b]		Migration Activity	Calcium Mobilization	Anti-HIV Activity (IC_{50}, nM)[c]	Type of Modulator and References
		SDF-1α	12G5				
CTCE-9908		ND	ND	−	ND	ND	Dimerized/Bivalent/ Orthosteric Modulator [188-190]
CXCL122		166	ND	−	+	ND	Dimerized/Bivalent/ Orthosteric Modulator [104, 174, 191]
TN14003	H-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-D-Lys -Pro-Tyr-Arg-Cit-Cys-Arg-NH_2[a]	ND	ND	−	ND	140	Cyclic/Orthosteric Modulator [179, 192]
BKT140 (4F-benzoyl -TN14003)	4-fluorobenzoyl-Arg-Arg-Nal-Cys-Tyr-Cit-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2[a]	0.99	ND	−	−	ND	Cyclic/Orthosteric Modulator [130, 193]
ATI-2341	Palmitic acid-MGYQKKLRSMTDKYRL	ND	ND	+	+	ND	Linear Peptide Modulator [168, 194]

[a] Each peptide has a disulfide linkage between Cys**4** and Cys**13**.

[b] Competition binding assays utilized a single concentration of radioiodinated SDF-1α or monoclonal antibody 12G5 in the presence of various concentrations of unlabeled chemokines.

[c] Infectious virus and/or single-cycle focal infective assays were performed to test the antiviral activities of CXCR4 inhibitors.

[d] The D-amino acids are italicized.

[e] ND: Not determined

[f] +: Promotion

[g] −: Inhibition