

•Reviews•

The CXCL12 (SDF-1)/CXCR4 chemokine axis: Oncogenic properties, molecular targeting, and synthetic and natural product CXCR4 inhibitors for cancer therapy

ZHOU Yu¹Δ, CAO Han-Bo²Δ, LI Wen-Jun², ZHAO Li^{2*}

¹ Center For Drug Evaluation, China Food and Drug Administration, Beijing 100022, China;

² State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Carcinogenesis and Intervention, China Pharmaceutical University, Nanjing 210009, China

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[ABSTRACT] Chemokine 12 (CXCL12), also known as stromal cell derived factor-1 (SDF-1) and a member of the CXC chemokine sub-family, is ubiquitously expressed in many tissues and cell types. It interacts specifically with the ligand for the transmembrane G protein-coupled receptors CXCR4 and CXCR7. The CXCL12/CXCR4 axis takes part in a series of physiological, biochemical, and pathological process, such as inflammation and leukocyte trafficking, cancer-induced bone pain, and postsurgical pain, and also is a key factor in the cross-talking between tumor cells and their microenvironment. Aberrant overexpression of CXCR4 is critical for tumor survival, proliferation, angiogenesis, homing and metastasis. In this review, we summarized the role of CXCL12/CXCR4 in cancer, CXCR4 inhibitors under clinical study, and natural product CXCR4 antagonists. In conclusion, the CXCL12/CXCR4 signaling is important for tumor development and targeting the pathway might represent an effective approach to developing novel therapy in cancer treatment.

[KEY WORDS] CXCL12/CXCR4; Tumor; Targeted therapy; Plerixafor

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Introduction

Chemokines produced in distinct tissue microenvironments promote survival and migration of cancer cells. Chemokine (C-X-C motif) receptor 4 (CXCR4) is the most common chemokine receptor expressing in a variety of cancer cells. This receptor protein belonging to G protein-coupled

cell surface receptors family [1]. Stromal cell-derived factor-1 (SDF-1, CXCL12), the ligand of CXCR4, is mainly secreted by marrow stromal cells in adults. CXCL12/CXCR4 signaling plays an important role in many physiological and pathological processes. For example, CXCL12/CXCR4 regulates epithelial-mesenchymal transition (EMT) in oral squamous cell carcinoma, glioblastoma, and sacral chondrosarcoma [2-4]. CXCR4 inhibition leads to suppression in angiogenesis and metastasis of sacral chondrosarcoma [5]. CXCL12/CXCR4 signaling also regulates adhesion to actin polymerization and vascular endothelium, as well as accommodate migration beneath and underneath bone mesenchymal stem cells (BMSCs) in leukemia cells [6]. In addition, CXCL12/CXCR4 axis is crucial for drug resistance in cancer cells [7]. Herein, we will review the effects of CXCL12/CXCR4 axis in cancer development and progression as well as the potential of targeting this pathway for cancer therapy.

Role of CXCL12/CXCR4 in Cancer Development

CXCL12/CXCR4 regulates survival and proliferation of cancers

CXCL12/CXCR4 signaling plays an important role in proliferation of cancer cells. Joseph MD *et al.* have detected

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[*Corresponding author] Tel/Fax: 86-25-83271055, E-mail: zhaoli@cpu.edu.cn

ΔThese authors contributed equally to this work.

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CXCR4 expression in pancreatic intraepithelial neoplasia (PanIN) tissues and demonstrated that CXCR4 could induce proliferation *via* activating Akt and ERK signaling in both murine and human pancreatic cancer cells [8]. As one of the most malignant and aggressive brain tumors, glioblastoma (GBM) has brought great harm to patients. In GBM, CXCL12/CXCR4 axis causes a significant increase in cell proliferation and survival, which can be reversed by blockage of CXCR4 [9]. Thompson *et al.* also have reported that CXCR4 mediates the proliferation of glioblastoma progenitor cells [10]. Barbieri *et al.* have highlighted that CXCL12/CXCR4 interaction plays a pivotal role in meningioma cell proliferation *via* activating ERK1/2 pathway [11]. Down-regulation of CXCR4 significantly reduces the cell proliferation by inhibiting PI3K/AKT/NF- κ B signaling pathway, and remarkably increases cell apoptosis in osteosarcoma cells [12]. A report has revealed that inhibition of CXCR4 and CXCR7 reduces the proliferation of human endometrial cancer and the targets could be useful for the treatment of the carcinoma [13]. In ovarian cancers, CXCL12/CXCR4 signaling significantly promotes cancer proliferation, migration, invasion, and peritoneal metastasis [14]. It is safe to say that the Notch-targeted approach effectively prevents myeloma cell migration, proliferation and resistance to apoptosis by reducing CXCR4 and CXCL12 level [15]. Also, in uveal melanoma (UM), the signaling promotes UM cell proliferation and migration. Liu *et al.* have found the CXCR4-shRNA interfering vector specifically inhibits CXCR4 expression and the proliferation, adhesion, and migration of human breast cancer cells MDA-MB-231 [16]. What's more, CXCR4 regulates cell proliferation and survival in laryngeal squamous carcinoma cells [17], human hilar cholangiocarcinoma [18], and human esophageal carcinoma cells [19]. Overall, CXCL12/CXCR4 axis is important for the survival and proliferation of various cancers.

CXCL12/CXCR4 regulates tumor angiogenesis

Among the factors involved in tumor angiogenesis, vascular endothelial growth factor (VEGF) is validated to be the closest one which can drive angiogenesis through binding with its natural receptor VEGFR2 [20-21]. VEGF expression has been found to be more pronounced in CXCR4 expressing cancer cells. CXCL12/CXCR4 signaling can increase VEGF-A promoter activity, promote angiogenesis, and enhance cancer cell viability [22]. Liang Z *et al.* have reported that CXCL12/CXCR4 signaling axis induces angiogenesis and progression of cancers by increasing expression of VEGF through the activation of PI3K/Akt pathway [23]. CXCL12/CXCR4 induces secretion of VEGF in normal human megakaryoblasts in a PI3K/Akt/NF- κ B dependent manner [24]. Claudio Napoli *et al.* have reported that CXCR4 plays a major role in neoangiogenesis to promote cancer progression, and inhibition of CXCR4/“Yin Yang 1” (YY1) leads to impairing VEGF network and angiogenesis during malignancy [25]. In addition, hypoxia-inducible factor 1 (HIF-1) and VEGF may up-regulate CXCR4 in glioblastoma, which promotes tumor an-

giogenesis [26]. Also, VEGF up-regulates CXCL12 and CXCR4 mRNA expression, and contributes to U251 cell invasion [27].

Endothelial progenitor cells (EPCs) are pluripotent stem cells, which have the potential to differentiate into mature endothelial cells. They are very important in tumor angiogenesis. Recent evidence has demonstrated that the CXCL12 has a major role in the recruitment and retention of CXCR4⁺ Bone Marrow cells to the neo-angiogenic niches, resulting in revascularization of tumors. In addition, CXCR4 is expressed on EPCs, which can direct the cells migrate to tumors to induce angiogenesis [28]. CXCL12/CXCR4 signaling also inhibits apoptosis and induces proliferation of EPCs [29]. What's more, CXCL12/CXCR4 axis induces the differentiation, spouting, and tube formation of EPCs. Yu P *et al.* have reported that CXCL12/CXCR4/PI3K/p-Akt signaling pathway increases progesterone-induced EPC viability [30]. Also, adenosine increases the migration of EPCs *via* increasing the expression of CXCR4 [31]. Above all, CXCL12/CXCR4 signaling can promote tumor angiogenesis by increasing VEGF expression and influencing EPCs functions.

CXCL12/CXCR4 participates in cancer metastasis

Metastasis to main organs is the key cause of death among cancer patients and many factors are involved in cancer invasion, such as TGF- β , E-cadherin, and Wnt/ β -catenin. The CXCL12/CXCR4 axis is also involved in metastasis of many human cancers. A previous study has shown that cancer cell invasion is reduced when CXCR4 neutralizing antibody is used or CXCR4 is knockdown [32], suggesting that CXCR4 expression is essential for cancer invasion. Kim *et al.* have detected the expression of CXCR4 in colorectal cancer patients with liver metastasis [33]. CXCR4 is also a chemokine receptor involved in the homing of metastatic breast cancer. It is highly expressed in breast cancer cells, contributing to cells tropism and invasion of the sites which secrete CXCL12, like lymph nodes, lungs, bone, and liver [34]. Yu T *et al.* have revealed that CXCR4 promotes Tca8113 migration and invasion by regulating MMP-9 and MMP-13 expression, perhaps *via* activation of the ERK signaling pathway [35]. In addition, PDZ-RhoGEF (PRG) regulates the migration and invasion of breast cancer cells in response to CXCL12, which is tightly correlated with the spatial regulation of Rho A activity [36]. Fontanella R *et al.* have shown that when cancer cells are treated with CXCR4 antagonist AMD3100, a reduction in their migration and invasion ability is observed [37]. Another study has shown that miR-494 suppresses the progression of breast cancer through Wnt/ β -catenin signaling pathway, which is mediated by CXCR4 [38]. In a 3D microenvironment model, interstitial flow enhances cell motility, CXCR4 activation, and CXCL12-driven brain cancer invasion [39]. In summary, the chemokine CXCL12 and its receptor CXCR4 play a major role in cancer invasion and metastasis, indicating that CXCR4 may be the target for the treatment of metastatic cancers.

CXCL12/CXCR4 plays an important role in transformation of inflammatory carcinoma

Inflammation has been appropriately added to the list of

hallmarks of cancer [40]. Pro-inflammatory cytokines are critical regulators of tumor microenvironment. They control proliferation of cancer cells and promote inflammation, tumor angiogenesis, and metastasis. Chemokines and their receptors are now known to play important roles in inflammation, infection, tissue injury, allergy, cardiovascular diseases, and malignant tumors [41]. A previous study has shown that IL-1 β and IL-1R1 promote cancer growth and metastasis by up-regulating CXCR4 expression and that CXCR4 may be a link between inflammation and cancer [42]. Furthermore, HIF-2 α that modulated macrophage migration by regulating the expression of the CXCR4 directly regulates pro-inflammatory cytokine/chemokine expression in macrophages activated *in vitro* [43]. Another study has revealed that CXCR4 antagonist significantly reduces local inflammation and significantly inhibits cancer cell growth, resulting in improved survival of the cancer-bearing mice [44]. So, CXCL12/CXCR4 may substantially improve cancer cell survival through promoting inflammation and tumor growth. In addition, resistin (an important player in inflammatory responses, and emerging as a mediator in inflammation-associated cancer) can upregulate the level of CXCL12, leading to activation of TLR4, p38 MARK, and NF- κ B signaling pathway in gastric cancer cells [45]. Above all, in the tumor microenvironment, inflammatory cells and molecules influence almost every aspect of cancer progression and CXCL12/CXCR4 plays a critical role in the process.

CXCL12/CXCR4 is a key axis in tumor microenvironment

As described above, CXCL12/CXCR4 pathway regulates cancer cell proliferation, metastasis and angiogenesis. It also plays a key role in tumor microenvironment cross-talk in several solid tumors. As a G protein-coupled receptor, CXCR4 binds to its ligand CXCL12 to trigger different downstream signaling pathways in cancer cells and in cells of the surrounding microenvironment, which result in a variety of cellular responses including angiogenesis, metastasis, proliferation, and survival [46-47]. CXCL12/CXCR4 can promote the progression of cancers by directly enhancing cancer growth and by influencing tumor microenvironment, such as recruiting EPCs to cause tumor angiogenesis [48]. Also, carcinoma-associated fibroblasts can secrete CXCL12, leading to cancer development in both paracrine and endocrine manner in the tumor microenvironment. In fact, CXCR4 is expressed in several cell types in the microenvironment, such as lymphocytes, hematopoietic stem cells, endothelial cells, and epithelial cells [47]. Hypoxic environment enhances CXCR4 expression through activation of HIF-1 α in cancer cells and stromal cells, leading to further development of cancer [49]. So CXCR4 may be a target both in cancer cells and the surrounding stromal, providing a new strategy for efficient cancer therapy. Besides hypoxia, inflammatory cells and inflammatory factors in the tumor microenvironment can induce the expression of a variety of cytokines to promote cancer progression. A published study has evaluated the effect of inhibition of CXCR4 in xenograft mouse model of inflammatory breast cancer and the

results show that inhibition of CXCR4 reduces primary tumor growth and metastasis [50]. Katoh H *et al.* have reported that the subsequent up-regulation of CXCL12/CXCR4 signaling facilitates cancer stromal formation by accelerating the recruitment of fibroblasts, resulting in cancer growth [51]. They have revealed that COX-2 and prostaglandin EP3/EP4 regulate the tumor stromal pro-angiogenic microenvironment *via* CXCL12/CXCR4 chemokine systems.

CXCL12/CXCR4 promotes development of hematologic malignancies

CXCR4 is normally expressed in T and B lymphocytes, monocytes, macrophages, neutrophils, and eosinophils. Pathological CXCR4 overexpression has been reported in hematopoietic malignancies such as leukemia and lymphoproliferative malignancies [52]. Bone marrow microenvironment plays critical roles in leukemogenesis, leukemia stem cell (LSC) survival, and drug resistance [53-55]. CXCL12/ CXCR4 axis is an important biological process for bone marrow microenvironment and is governed by a cascade of molecular interactions. The level of CXCR4 is significantly elevated in leukemic cells from patients with AML [56], and is closely related to poor prognosis [57-58]. CXCL12, which secreted from bone marrow cells, can induce CML cells to resist tyrosine kinase inhibitors (TKI) therapy from multiple aspects, such as the directional migration, adherence to marrow cavity, the mediation of cell protective dormancy, activation of numerous survival signaling pathways, the suppression of mitochondrial-dependent apoptosis and the up-regulated expression of BCL-6. In addition, AMD3100, an inhibitor of CXCR4, is known to block the CXCL12/CXCR4 interaction, disrupts the interaction between cancer and matrix, mobilizes the leukemia cells to keep away from the protective microenvironment [59]. In order to keep with the myeloma cells origin, the cells express high level CXCR4 and require stromal expression of CXCL12 for homing and niche maintenance, and AMD3100, clinically used for hematopoietic stem cells (HSCs) mobilization, has been proposed as an agent of inducing chemosensitivity in myeloma [60-61]. Nowadays, CXCR4-targeted endoradiotherapy (ERT) is a new theranostic approach, and CXCR4-directed ERT with Lu-Pentixather is distributed to leukemia harboring organs, resulting in an efficient reduction of leukemia [62].

CXCL12/CXCR4 Mediates Drug-resistance

High expression of CXCR12 is also important in drug-resistance in cancer therapy [63-65]. Hu *et al.* have reported that up-regulation of CXCR4 mediates Gefitinib-resistance in cross-talk with EMT in non-small cell lung cancer (NSCLC) [66]. CXCL12/CXCR4 axis also confers Adriamycin and Imatinib resistance in human chronic myelogenous leukemia in the BM microenvironment [65]. In pancreatic cancers, CXCL12/ CXCR4 axis also leads to the resistance to Gemcitabine [67]. In Gemcitabine-resistance PaCa cells, Gemcitabine induces the expression of CXCR4, but not in GEM-sensitive PaCa

cells. This study has demonstrated that CXCL12/CXCR4 signaling really influences resistance to gemcitabine in PaCa cells [67]. Synthetic Exosome-Like Nanoparticles (SELN) can activate NF-κB, which regulates the expression and secretion of CXCL12. The interaction of CXCL12 and CXCR4 further activates Akt survival pathway to protect cells from death. So CXCL12/CXCR4 axis can promote the development of cancers, which has implications in drug resistance [68]. In bone marrow-disseminated cancer cells, with TGF-β2 being down-regulated, CXCL12/CXCR4 signaling is also inhibited. As a result, inhibition of CXCR4 reverses the drug resistance of BM-HEp3 cells. So, TGF-β2-triggered CXCL12/CXCR4 signaling is important for drug resistance [7]. In addition, ErbB-2-overexpressing cells become resistant to the anti-ErbB-2 agent Lapatinib by activating alternative mechanisms of controlling proliferation, such as Src and CXCR4 signaling. Blockade of CXCR4 represents a novel therapeutic intervention in Lapatinib-resistant breast cancer patients [69]. In Schultz's study [70], Tamoxifen-resistant cells have a higher percentage of cancer progenitor cells that are responsive to CXCR4 inhibition. Inhibition of CXCR4 or AhR with small molecule antagonists specifically target cancer stem-like cell populations in MCF7 cells and could be beneficial to the treatment of Tamoxifen-resistant breast cancer. In another study, drug-resistant colorectal cancer cells show an increased expression of CD133 and CXCR4. Lymph node stromal cells can secrete CXCL12 which interacts with CXCR4 on colorectal cancer cells and then enhances drug-resistance [71]. Above all, CXCL12/CXCR4 signaling is critical for drug-resistance in cancers, which may be an important target for cancer therapy.

Considering other signaling pathways involved in the biological effects of CXCL12/CXCR4, we compile the relevant pathways in Fig. 1.

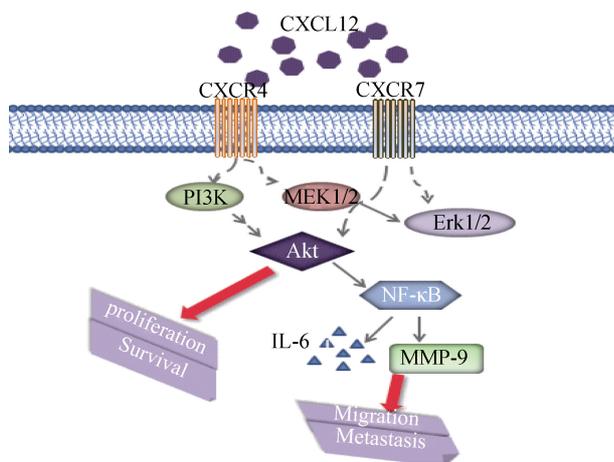


Fig. 1 CXCL12/CXCR4 related pathways

Anti-cancer Agents Targeted CXCL12/CXCR4 Axis

Anti-cancer effects of synthetic drugs targeting CXCR4

As we know, chemokines and chemokine receptors regulate multiple physiological and pathological processes, such

as morphogenesis, angiogenesis, immune responses and cancers. Among the multitudinous chemokine receptors, CXCR4 stands out for its pleiotropic roles. CXCR4 is expressed in at least 20 different human cancers, including cancer cells from brain neoplasm (neuronal and glial cancers) [72-73], neuroblastoma cells [74], colorectal cancer [71], prostate cancer [75], melanoma [76], breast cancer [77], ovarian cancer [78], and leukemia [56], among others. CXCL12, the ligand of CXCR4, is usually secreted in the tumor microenvironment by stromal cells and other cells. It can be combined with CXCR4 to activate the downstream signaling pathway to promote cancer development. Therefore, it has been thought that CXCR4 antagonism could prevent the development of cancers by targeting multiple steps in the process. Here in we summarize the anti-cancer agents targeting CXCL12/CXCR4 axis, and the information on CXCR4 antagonists is listed in Table 1.

Plerixafor is the only drug currently used in the clinic. It was launched for NHL and MM patients in the US in December 2008 and launched in the EU August 2009. In January 2016, the drug was filed for Japanese approval for enhancing hematopoietic stem cell mobilization for autologous transplantation, blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). In the EU, the drug is indicated in combination with G-CSF to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and MM whose cells mobilize poorly. Finally, plerixafor lacks CXCR4 specificity because it also binds the other CXCL12 receptor, CXCR7, as an allosteric agonist [79]. Recent studies have found that Plerixafor is also used in other treatments, such as promoting proliferation of Ewing sarcoma cell lines *in vitro* and activates receptor tyrosine kinase signaling [80] and mobilizing CD56 bright NK cells in blood, providing an allograft predicted to protect against GvHD [81].

A plurality of natural products' versatile use of CXCL12/ CXCR4

The anti-cancer activity of a large number of currently studied flavonoid compounds is also affected by the biological activity of CXCR4/CXCL12. Quercetin-3-O-glucuronide, Quercetin, apigenin, Luteolin, Oroxlylin A and Silymarin have anti-cancer effects through the inhibition of CXCR4 [65, 82-86]. Naringin, a major active ingredient in the Chinese herb *Drynaria fortunei*, can promote angiogenesis and inhibit endothelial cell apoptosis through the CXCL12/CXCR4/PI3K/Akt signaling pathway [87]. Puerarin, an isoflavone derivative, could significantly inhibit lipopolysaccharide (LPS)-induced MCF-7 and MDA-MB-231 cell migration, invasion and adhesion by regulating the expression of CCR7, MMP-2, MMP-9, ICAM, and CXCR4 [88]. IND02, a type A procyanidin polyphenol extracted from cinnamon, which is a bioflavonoid derivative that features trimeric and pentameric forms, displays an anti-HIV-1 activity against CXCR4 and CCR5 viruses [89]. Prenylated flavonoids glyceollins inhibit the function of EPCs in tumor neovascularization by inhibit-

ing the mRNA expression of SDF-1 and CXCR4 [90]. Flavonoids, flavanones, isoflavones, bioketides, and prenylated fla-

vonoids can produce anticancer and antiviral effects by modulating the SDF-1/CXCR4 axis.

Table 1 Synthetic CXCR4 antagonists under clinical investigation

Drug Name	Other drug names	Target-based Actions	Active companies	Active indications	Highest status
Plerixafor [48]	AMD-3100; GZ316455; JM-3100; Mozobil; SDZ-SID-791; SID-791	CXCR4 chemokine antagonist; Neoplastin inhibitor	Sanofi; Sanofi Genzyme	Chronic lymphocytic leukemia; Diabetic foot ulcer; Glioma; Neutropenia; Non-Hodgkin lymphoma; Sickle cell anemia	Launched
USL-311 [56]	Proximagen	CXCR4 chemokine antagonist	Proximagen Group plc	Glioblastoma; Inflammatory disease; Solid tumor	Phase 2 Clinical
LY-2510924 [76]	CXCR4 peptide inhibitor (cancer)	CXCR4 chemokine antagonist; Stromal cell-derived factor 1 ligand inhibitor	Eli Lilly & Co	Renal cell carcinoma; Small-cell lung cancer	Phase 2 Clinical
Ulocuplumab [73]	BMS-936564; MDX-1338	CXCR4 chemokine antagonist	Bristol-Myers Squibb Co	Advanced solid tumor; Cancer	Phase 2 Clinical
BL-8040 [78]	TG-0054; bulishafu; burixafor	CXCR4 chemokine antagonist	BioLineRx Ltd	Acute myelogenous leukemia; Aplastic anemia; Bone marrow transplantation; Metastatic pancreas cancer; Multiple myeloma; Myelodysplastic syndrome; Thrombocytopenia	Phase 2 Clinical
Burixafor [80]	TG-0054; bulishafu	CXCR4 chemokine antagonist	TaiGen Biotechnology Co Ltd	Age related macular degeneration; Diabetic retinopathy; Ischemia; Leukemia; Myocardial infarction; Ocular disease; Stem cell transplantation	Phase 2 Clinical
Balixafortide [81]	Polyphor; POL-2438; POL-3026; POL-6326; POL-6326	CXCR4 chemokine antagonist	Polyphor Ltd	Cancer; Inflammatory disease; Myocardial infarction; Stem cell transplantation; Wound healing	Phase 2 Clinical
PTX-9908 [67]	CTCE-9908; CTCE-9908/0019; PTX-9908;	CXCR4 chemokine antagonist; Stromal cell-derived factor 1 ligand inhibitor	MicroConstants China; Pertinax Therapeutics Inc	Cancer; Lupus nephritis	Phase 2 Clinical
X4P-001 [83]	AMD-11070	CXCR4 chemokine antagonist	X4 Pharmaceuticals Inc	Cancer; Melanoma; Renal cell carcinoma	Phase 1 Clinical
GMI-1359 [69]	GMI-1215; w	CXCR4 chemokine antagonist; Cell adhesion molecule inhibitor; E-Selectin antagonist	GlycoMimetics Inc	Cancer; Inflammatory disease	Phase 1 Clinical
UMK121 (filgrastim + plerixafor) [79]	Proteonmix	CXCR4 chemokine antagonist; GCSF ligand; GCSF receptor agonist	Proteonmix Inc	Bone marrow transplantation; Cancer; Heart disease; Liver disease	Phase 1 Clinical
F-50067 [68]	515H7; hz-515H7	CXCR4 chemokine antagonist; Stromal cell-derived factor 1 ligand inhibitor	Pierre Fabre SA	Cancer	Phase 1 Clinical
Radiolabeled pentixather [58]	177Lu-pentixather; 90Y-pentixather;	CXCR4 gene modulator	Technical University of Munich; University of Wurzburg	Multiple myeloma	Clinical

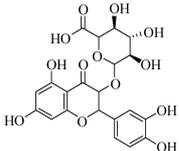
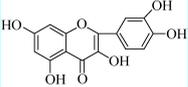
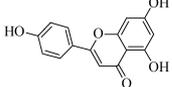
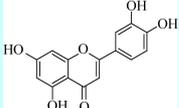
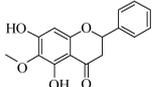
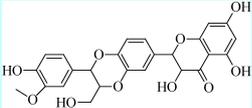
In addition to the natural products of flavonoids, other natural products also have a regulatory effect on CXCR4. CXCR4 is deeply involved in several pathologies, such as HIV infection, rheumatoid arthritis, cancer development, progression, and metastasis. Nowadays, many natural products have been found to inhibit the biological axis of CXCL12/

CXCR4. Chen *et al.* have reported that Ginsenoside Rg3 regulates migration of a breast cancer cells by inhibiting CXCR4 expression at a dosage without obvious cytotoxicity [91]. Two chloroform extracts of *Ficus deltoidea*, FD1c and FD2c are able to inhibit cell migration and invasion by modulating the CXCL12-CXCR4 axis in human prostate cancer PC3 cells

[92]. Penicillixanthone A (PXA), a natural xanthone dimer from jellyfish-derived fungus *Aspergillus fumigates* obtained from marine-derived, displays potent anti-HIV-1 activity by inhibiting infection against CCR5-tropic HIV-1 SF162 and CXCR4-tropic HIV-1 NL4-3 [93]. *Urtica dioica* extract can inhibit the ability of miR-21 to inhibit the proliferation and metastasis of breast cancer cells by down-regulating the expression of CXCR4 and other genes [94]. Methanolic extract of *Boswellia serrate* inhibits proliferation, angiogenesis, and migration and induces apoptosis in HT-29 cells by inhibiting of mPGES-1 and decreasing the CXCR4 level and its downstream targets [95]. “Yi Guan Jian” decoction may induce the differentiation of bone marrow mesenchymal stem cells (BMSCs) into hepatocyte-like cells (HLCs) to reverse dimethylnitrosamine-induced liver cirrhosis; this may be achieved via an

upregulation of the SDF-1/CXCR4 axis to activate the mitogen activated protein kinase/ERK1/2 signaling pathway [96]. Treatment with *Hormophysa triquerta* polyphenol, an elixir, significantly inhibits the migration and invasion of pancreatic cancer cells induced by ionizing radiation by inhibiting the expression of CXCR4/COX-2, thus providing a new idea for drug treatment of treatment-resistant pancreatic cancer cells [97]. Pak *et al.* have reported that anticancer effects of herbal mixture extract in the pancreatic adenocarcinoma PANC1 cells are mediated by inhibiting the expression of apoptosis-associated genes (CXCR4, JAK2, and XIAP) and stem cell-associated genes (ABCG2, POU5F1, and SOX2) [98]. In summary, the anti-cancer activity of many natural products is achieved by inhibiting the CXCL12/CXCR4 axis. Natural product CXCR4 antagonists under clinical investigation are summarized in Table 2.

Table 2 Natural product CXCR4 antagonists under clinical investigation

Drug Name	Chemical structure	Target-based action	Active indication
Quercetin-3- <i>O</i> -glucuronide [82]		inhibition of CXCR4, promotes the proliferation and migration	AML, neural stem cells, H2O2-induced injury of feline esophageal epithelial cells
Quercetin [83]		inhibition of CXCR4, Inhibit RPS19 and contributes to metastasis	Androgen Receptor Signaling and Inhibits Prostate Cancer, 431-III cells
Apigenin [84]		inhibition of CXCR4, Inhibiting MAPK-Mediated AP-1 and NF-κB Signaling, interfering with cell cycle and inducing apoptosis	Human Bladder Cancer T24 Cells, NCI-H460 and HCT-15 cells, HT-29 human colon cancer cell line
Luteolin [86]		inhibition of CXCR4, blocking Akt/mTOR/c-Myc signaling pathway, JNK-mediated apoptosis	Bronchial Asthma, Chronic obstructive pulmonary disease, Chronic pharyngitis, Allergic rhinitis
Oroxylin A [64]		inhibition of CXCR4 and Akt/MAPK/NF-κB pathways, activates PKM1/HNF4 alpha, reprogram of HIF1α-modulated fatty acid metabolism	Endothelial, CML cells, colorectal cancer, non-small cell lung cancer
Silymarin [85]		inhibition of CXCR4, antioxidant effect and EGFR/ERK1/2 signaling, actin cytoskeleton and PI3K/Akt signaling pathways	diethylnitrosamine-induced hepatocellular carcinoma, bladder cancer, CML.

Conclusions

More and more investigations on the biological effects of the CXCL12/CXCR4 pathway have been reported in recent years, especially with increasing interests in its physiological role. Targeting the CXCL12/CXCR4 axis may have several beneficial effects, including affecting CXCR4-expressing primary cancer cells, synergizing with other cancer-targeted therapies and modulating the immune response. Blocking CXCL12/CXCR4 signaling may reduce cancer cell invasion and metastasis and inhibit cancer cell growth, which can pro-

vide a new idea for cancer treatment. By inhibiting CXCL12/CXCR4, many natural medicines can achieve certain therapeutic effect as well. Surprisingly, newly reported results indicate that CXCL12 is able to promote the function of immune system [99-100], an inspiration for studying natural substances in the future. Natural compounds have nowadays attracted lots of interests among researchers. Thanks to their low toxicities and multi-targets in mechanisms of action, many natural medicines have little or no harm to normal cells and even protect them at the dose levels with inhibiting effects on cancer cell growth, providing more novel drug candidates for cancer therapy.

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