REVIEW

The biological role of the CXCL12/CXCR4 axis in esophageal squamous cell carcinoma

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ABSTRACT Esophageal cancer is the eighth most common malignant tumor and the sixth leading cause of cancer-related death worldwide. Esophageal squamous cell carcinoma (ESCC) is the main histological type of esophageal cancer, and accounts for 90% of all cancer cases. Despite the progress made in surgery, chemotherapy, and radiotherapy, the mortality rate from esophageal cancer remains high, and the overall 5-year survival rate is less than 20%, even in developed countries. The C-X-C motif chemokine ligand 12 (CXCL12) is a member of the CXC chemokine subgroup, which is widely expressed in a variety of tissues and cells. CXCL12 participates in the regulation of many physiological and pathological processes by binding to its specific receptor, C-X-C motif chemokine receptor type 4 (CXCR4), where it causes embryonic development, immune response, and angiogenesis. In addition, increasing evidence indicates that the CXCL12/CXCR4 axis plays an important role in the biological processes of tumor cells. Studies have shown that CXCL12 and its receptor, CXCR4, are highly expressed in ESCC. This abnormal expression contributes to tumor proliferation, lymph node and distant metastases, and worsening prognosis. At present, antagonists and imaging agents against CXCL12 or CXCR4 have been developed to interfere with the malignant process and monitor metastasis of tumors. This article summarizes the structure, function, and regulatory mechanism of CXCL12/CXCR4 and its role in the malignancy of ESCC. Current results from preclinical research targeting CXCL12/CXCR4 are also summarized to provide a reference for the clinical diagnosis and treatment of ESCC.

KEYWORDS Esophageal squamous cell carcinoma; C-X-C motif chemokine ligand 12; CXC chemokine receptor 4; antagonists; imaging agent

Introduction

Esophageal cancer is the eighth most common cancer worldwide[1,2], and includes the following two main tissue subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. ESCC, which is the main histological type of esophageal cancer, accounts for approximately 90% of cases worldwide[1]. In recent years, the mortality rate from esophageal cancer has remained high despite advances in surgical techniques, chemotherapy, and radiotherapy strategies. Most patients are diagnosed at an advanced stage, often with lymph node or distant metastasis, and the 5-year survival rate is less than 20%, even in developed countries[3-5]. However, the 5-year survival rate in patients with early diagnosis can be considerably improved using endoscopic or surgical treatment[6]. Therefore, identifying a biomarker that can predict tumorigenesis at an early stage would be very advantageous.

The human chemokine system contains approximately 50 different chemokines and 20 chemokine receptors[7]. Chemokines are soluble small molecule secretory proteins with a molecular weight of approximately 8 kDa. According to the position of their cysteine residues, chemokines can be divided into 4 subgroups (CX3C, CXC, CC, and C, the C represents a cysteine residue, and the X/X3 represents 1 or 3 non-cysteine amino acids at conserved locations)[8,9]. Chemokine receptors are a class of 7 transmembrane spanning domains, G-protein coupled receptors (GPCR), characterized according to their preference for specific chemokines[10,11]. The C-X-C motif chemokine ligand 12 (CXCL12) is one of the most studied CXC chemokine ligands. CXCL12 participates in many aspects of tumor progression, including survival, proliferation,

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angiogenesis, and metastasis, by interacting with its CXCR4 receptor[12,13].

The molecular mechanisms involved in the origin and development of ESCC is unclear, and limit the effective treatment options available for this highly invasive tumor. However, in recent years, the role of the CXCL12/CXCR4 axis in ESCC has received increasing attention. Understanding such mechanisms will help to design new targeted therapies to block chemokine-induced metastasis and diffusion. This manuscript aims to describe the role of the CXCL12/CXCR4 axis in promoting the malignant processes in ESCC, and to describe antagonists and imaging agents available for targeting CXCL12/CXCR4, to help guide clinical diagnosis and treatment.

CXCL12/CXCR4 axis structure and function

The CXCL12 gene is located on chromosome 10q11 and has 6 different splice variants in humans, including α, β, γ, δ, ε, and ψ[14]. CXCL12 is a type of homeostatic chemokine, which was originally identified as a pre-B cell growth factor and was found to be essential for homeostatic maintenance[15,16]. CXCL12 is constitutively expressed by bone marrow stromal cells and is therefore referred to as stromal cell-derived factor-1[17]. CXCR4 is a member of the GPCR family, comprising 352 amino acid residues, and is expressed in hematopoietic stem/progenitor, pre-B, and endothelial cells[18-21]. CXCR4 is reported to be upregulated in at least 23 different hematopoietic and nonhematopoietic tumors, including esophageal cancer[22-37].

The CXCL12/CXCR4 axis is involved in embryonic development, immune and inflammatory responses, and stem cell migration and homing[38-43]. This axis is also involved in the malignant development of various tumors, by promoting proliferation, angiogenesis, invasion, and metastasis[44]. CXCL12 works synergistically with vascular endothelial growth factor to induce neovascularization by attracting endothelial progenitor cells into the tumor microenvironment, resulting in a sufficient oxygen supply for tumor maintenance[25]. CXCL12 can promote the tumor process in four ways: it can promote neovascularization and provide oxygen supply to tumor cells[45], it can directly promote tumor cell survival and proliferation in a paracrine manner[46], it can cause tumor cell metastasis by interacting with its receptor (CXCR4), and finally, CXCR4

positive tumor cells may have stem cell characteristics and therefore a high potential for metastasis[47,48].

Regulation of the CXCL12/CXCR4 axis in cancer

The expression of CXCL12/CXCR4 can be regulated at three levels: epigenetic, transcriptional, and post-transcriptional. Epigenetic silencing leads to an imbalance in CXCL12/CXCR4 expression, and hypermethylation of the CXCL12 promoter, which is related to its metastatic potential, and has been detected in various tumors[49-51]. However, loss of methylation from the CXCR4 promoter leads to upregulation of CXCR4 expression[52,53]. Tumor cells that maintain CXCR4 overexpression, but lack CXCL12 expression, can be directionally transferred to target organs with high levels of CXCL12 secretion.

Some studies have also found that CXCL12/CXCR4 is regulated by many factors at the transcriptional level. The CXCR4 gene promoter contains the hypoxia response element, and under hypoxic conditions, hypoxia-inducible factor-1 binds to the hypoxia response element region of the promoter, causing the induction of CXCR4 gene transcription and expression[54]. Furthermore, recent studies have reported that nuclear factor kappa-B promotes tumor growth by increasing the expression of CXCL12[55]. Matrix metalloproteinase 10 promotes angiogenesis, growth, and diffusion of human hepatocellular carcinomas by regulating the CXCL12/CXCR4 axis, and the phosphatase and tensin homolog can negatively regulate the expression of CXCL12/CXCR4 in prostate tumors, thereby controlling tumor growth[56-58]. In Jurkat T cells, the lipid phosphatase activity of the phosphatase and tensin homolog negatively regulates CXCR4-mediated chemotaxis. Other factors, such as transforming growth factor β[59], transcription factor 12[60], and vascular endothelial growth factor[61] have all been reported to control the expression of CXCR4, thereby regulating malignant tumor progression.

In addition to the two regulatory mechanisms previously mentioned, CXCL12 and CXCR4 can be regulated by microRNAs (miRNA) at the post-transcriptional level. MiRNAs are a group of highly conserved, small molecular weight noncoding RNAs that participate in the post-transcriptional regulation of gene expression by base complementarity at the 3′-UTRs of target mRNAs, leading to mRNA silencing or transcriptional inhibition[62]. Control of the expression of CXCL12 in cancer

cells is due to it being targeted by numerous microRNAs, and this targeting of the CXCL12/CXCR4 axis may inhibit the development and progression of tumors[63-67].

The CXCL12/CXCR4 signaling pathway

The interaction of CXCL12 with its G-protein coupled CXCR4 receptor causes dissociation of its heterotrimeric G protein into Gαi and Gβγ subunits and converts guanosine diphosphate to guanosine triphosphate[68]. Gαi inhibits cAMP production, and causes the inhibition of adenylate cyclase activation, resulting in the activation of downstream pathways, such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK)[40,69]. Gβγ activates phospholipase C (PLC), which causes the synthesis of diacylglycerol and inositol 1,4,5-triphosphate (IP3). Next, IP3 binds to specific receptors on the endoplasmic reticulum, causing the mobilization of Ca^{2+} from intracellular stores, resulting in a transient increase in intracellular Ca^{2+}[70]. This interaction induces the activation of various intracellular pathways, including PI3K-Akt, Ca^{2+}-dependent tyrosine kinases such as PYK2, and MAPK signaling pathways, such as P38, JNK, and ERK[71-73]. In addition, related studies have found that CXCL12/CXCR4 can also induce the Janus kinase signal and transcriptional activator (JAK/STAT) pathway independently of G-protein

involvement[74]. β-arrestin can also regulate the CXCR4 signaling pathway and mediate CXCR4 receptor internalization and desensitization[75,76]. CXCL12 can also mediate signal transduction through a different receptor, CXCR7. No classical GPCR-mediated signal transduction was observed when CXCR7 was activated by CXCL12; however, the β-arrestin pathway was activated and scavenging of CXCL12 was promoted[77]. CXCR7 can also improve cell survival through the PLC/MAPK signaling pathway[78]. In addition, CXCR7 can change the conformation of the CXCR4/G-protein complex, to form heterodimers with CXCR4, and abrogate the CXCR4-mediated signal transduction[79,80]. The CXCL12-mediated signaling pathway is shown in **Figure 1**.

Studies have also found that expression of CXCR4 in ESCC is higher than that in its corresponding normal tissues. CXCR4 also promotes tumor growth and invasion by activating the PI3K/AKT pathway and upregulating Rho family members[81]. However, the role of the CXCL12/CXCR7 signaling axis in ESCC is unclear.

The relationship between CXCR4 and ESCC

CXCR4 expression in ESCC

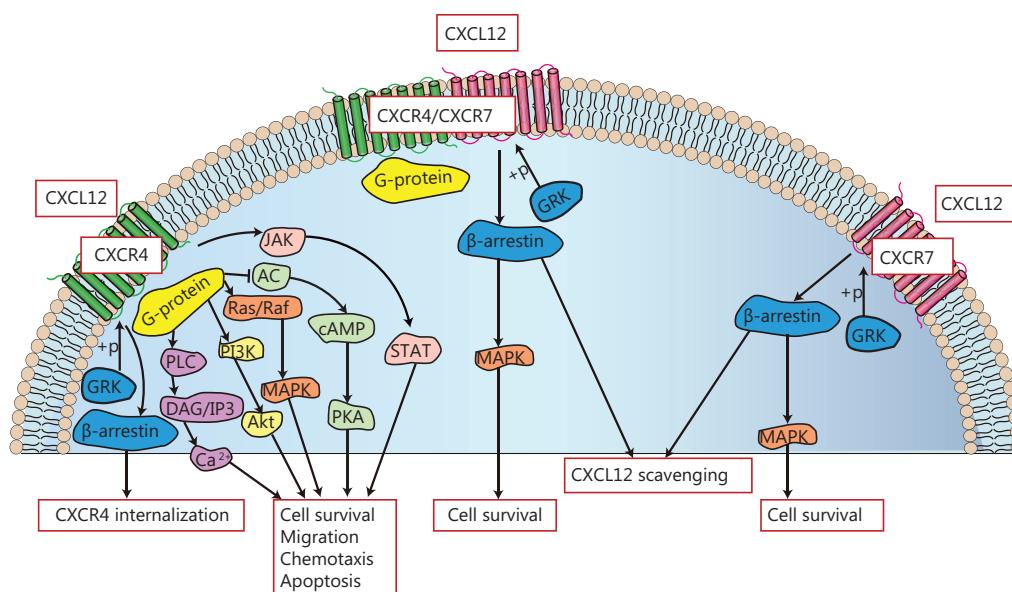CXCL12 and CXCR4 are expressed in ESCC, and the level of CXCR4 in primary and metastatic lesions is significantly

Figure 1 Schematic diagram of the CXCR12/CXCR4 signaling pathway.

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increased compared to normal tissues. The increased expression levels of CXCL12 and CXCR4 detected by immunohistochemistry in cancer tissues were 50%–78% and 61%–80%, respectively, showing significantly higher levels than found in the corresponding normal tissues[82,83]. Meta-analyses have found that CXCR4 was significantly expressed in ESCC when compared to normal tissues[84]. CXCR4 is a 7 transmembrane spanning domain receptor, and studies have found that it is mainly expressed in the cytoplasm and nucleus[22]. This phenomenon may be due to the activation of CXCR4 by CXCL12 and its translocation from the cell membrane to the cytoplasm, thereby inducing CXCR4 internalization and specific downstream signals. The expression profiles of CXCL12 and CXCR4 are closely related to the biological behavior of ESCC. The expression of CXCL12 affects multiple phenotypes in ESCC, including tumor stage, lymphatic invasion, and distant metastases[83]. The expression of CXCR4 in primary tumors is positively correlated with micrometastases to the lymph nodes and bone marrow, and negatively correlated with overall disease-specific survival[85,86]. Lukaszewicz-Zajac et al.[87] showed that the concentrations of serum CXCL12 and CXCR4 in patients with esophageal cancers were significantly higher for CXCL12, but significantly lower for CXCR4, when compared to healthy controls. This increase in serum CXCL12 concentration and the concomitant decrease in its receptor may lead to enhancement of the binding capability of CXCR4 for CXCL12.

CXCR4 promotes ESCC cell metastasis

ESCC is a highly invasive and metastatic tumor with a high tendency for lymph node metastasis. Metastasis of ESCC may involve the CXCR4 receptor because of its unique metastatic pattern and the high constitutive expression of CXCL12 at these metastatic sites[88,89]. Studies have found that CXCR4 is a major chemotactic receptor that mediates lymph node and distant organ metastases in ESCC[90]. The inhibition of CXCR4 with shRNA can significantly reduce the metastatic and proliferative potentials of esophageal cancer[91].

CXCR4 positive tumor cells metastasize to organs with high expression of CXCL12, such as lymph nodes, liver, lungs, and bone marrow[88,89]. Clinical data from ESCCs have found that the expressions of CXCL12 and CXCR4 are closely related to increased lymph node metastasis, and further studies have confirmed that CXCL12/CXCR4 promotes lymph node metastasis[86]. CXCL12 is highly expressed in lymph nodes and can stimulate lymphangiogenesis by inducing the migration of lymphangiogenic endothelial cells. The expression of CXCR4 is upregulated in lymphangiogenic endothelial cells, but the expression level is low in mature lymphatic vessels[92].

The role of CXCR4 in ESCC cell proliferation

In addition to metastasis, the CXCL12/CXCR4 signaling pathway also contributes to the growth and proliferation of ESCC[93]. When the CXCR4 knockdown cell line, Eca109, was inoculated subcutaneously into BALB/c-nu/nu mice, the tumor mass formed at the inoculation site was significantly smaller than the control group. Moreover, *in vitro* experiments showed that the proliferative capability of Eca109-shCXCR4 cells was significantly lower than that of the parent or control cells. The proliferative capability of human esophageal epithelial cells overexpressing CXCR4 was increased when compared to the control group[81].

The molecular mechanisms by which CXCR4 promotes tumor growth have been widely studied and are summarized as follows: (1) CXCL12 produced in the tumor microenvironment allows the entrance of circulating endothelial progenitor cells to the primary tumor site and produces additional microvessels, thereby increasing the oxygen supply to the tumor[14,94]. (2) Common signaling pathways related to cell proliferation, such as PI3K/AKT, Src/ERK1-2, and STAT3, are activated[81,95,96]. (3) CXCR4/CXCL12 signaling participates in Treg cell bone marrow homing and plasmacytoid dendritic cell trafficking, suppressing antitumor immunity, and promoting tumor growth[97-99].

CXCR4 and ESCC prognosis

Studies have evaluated the effect of CXCR4 expression on ESCC prognosis. Gockel et al.[100] found that the median survival time for patients with high expression of CXCR4 was 20 months, whereas patients with low expression was 76 months, and this difference was statistically significant ($P < 0.05$). Furthermore, Wu et al.[101] conducted a meta-analysis comprising 1,055 participants from Germany, China, and Japan. Their results showed that overexpression of CXCR4 was related to tumor depth ($P < 0.01$), lymph node status ($P < 0.01$), tumor node metastasis stage ($P < 0.01$), and histological type ($P = 0.03$). They also found that the overexpression of CXCR4 significantly decreased the overall survival rate

($P < 0.01$). CXCR4 therefore appears to be a reliable prognostic marker for ESCC.

In vivo and *in vitro* studies have shown that lentiviral shRNA-induced CXCR4 gene silencing can inhibit the proliferation and metastasis of ESCC cell lines[91]. However, the specific mechanism by which CXCR4 promotes the malignant development of ESCC is unclear. Recent studies have found a rare population of tumor cells whose characteristics are like stem cells. These cells have been referred to as cancer stem cells (CSCs), which mediate tumor growth, metastasis, recurrence, and therapeutic drug resistance. CXCR4 is highly expressed in esophageal tumor stem cells, and the expression of CXCR4 in CSCs increases the malignant potential of ESCC and is associated with ESCC recurrence and metastasis[102]. CD133+ esophageal CSCs contain a subgroup of cells characterized by the co-expression of CXCR4 and can evade the primary tumor and establish distant metastasis[47].

Future therapeutic directions

The overexpression of CXCR4 in tumor tissue is related to tumor proliferation, tumor invasion, increased risk of metastasis, and poor survival outcomes. Many small molecule CXCR4-based inhibitors have been developed because of the important role of CXCR4 in oncology. These inhibitors have been reviewed in several studies. CXCR4 antagonists can be divided into the following 4 categories: small peptide CXCR4 antagonists, non-peptide CXCR4 antagonists, antibodies against CXCR4, and SDF-1-modified agonists and antagonists.

AMD3100 (Mozobil™) was originally designed for the treatment of AIDS[103,104]. However, an increase in leukocyte count was observed in phase I clinical trials after AMD3100 administration. Further studies found that AMD3100 could mobilize CD34+ hematopoietic stem cells in peripheral blood and when combined with granulocyte colony-stimulating factor, could recruit more CD34+ cells than granulocyte colony-stimulating factor alone[105,106]. The US Food and Drug Administration (FDA) has currently approved AMD3100 for the treatment of patients with hematological malignancies[106].

CTCE-9908 is a small peptide analog designed to antagonize the CXCR4 receptor and can reduce the lung metastasis of osteosarcoma and melanoma cells in a mouse model[107]. CTCE-9908 has been tested in phase I/II clinical trials as monotherapy for solid tumors. In July 2005, the FDA approved CTCE-9908 as an orphan drug for the treatment of osteosarcoma.

Olaptesed Pegol (NOX-A12) is an L-stereoisomer RNA oligonucleotide, linked to 40 kDa polyethylene glycol, and this anti-CXCL12 compound can bind and neutralize CXCL12 with high affinity and specificity. NOX-A12 mobilizes hematopoietic stem cells and leukocytes from the bone marrow to the periphery[108]. In 2014, NOX-A12 combined with radiotherapy was approved by the FDA for the treatment of malignant glioma and is currently being tested in phase IIa clinical trials for the treatment of multiple myeloma and chronic lymphoblastic leukemia[109,110]. In addition, other CXCR4 inhibitors are in different stages of clinical trials (**Table 1**).

CXCR4 antagonists play an important role in sensitizing tumor cells to chemotherapy, and existing imaging agents targeting CXCR4 have the potential to guide and monitor cancer treatment. The overexpression of CXCR4 in cancer directly affects the chemotaxis of tumor cells to the SDF-1 gradient. Highly expressed CXCL12 has been found in the most common sites of tumor metastasis, including lymph nodes, lung, liver, and bone marrow. Thus, the application of CXCR4 in the field of diagnostic oncology has received increasing attention. Nimmagadda et al.[111] used Iodine-125-labeled anti-CXCR4 monoclonal antibody to develop CXCR4-targeted tracers. Hanaoka et al.[112] revealed that the peptide antagonist, Ac-TZ14011, labeled with Indium-111 is a potential agent for imaging the expression levels of CXCR4 in metastatic tumors *in vivo*. In addition, AMD3100 has been labeled with copper 64 to visualize CXCR4-positive tumor cells *in vivo* and can be used to guide and monitor anti-CXCR4 tumor treatment[113]. Several other agents, such as CXCL12-based imaging agent and bioluminescence, have been developed for tumor diagnostic imaging[114-116].

For locally advanced and unresectable ESCC patients, the combination therapy of fluoropyrimidine-based and platinum-based drugs is the first-line treatment. Persistent high expression of CXCR4 after chemoradiotherapy predicts tumor recurrence and poor prognosis[117]. Blocking the CXCL12-CXCR4 axis can enhance the sensitivity of tumor cells to chemotherapy drugs and reduce tumor volume[82,93,118,119]. In addition, it has been reported that AMD3100 can regulate immunosuppression in tumors[120,121]. These results indicate that blocking the CXCL12/CXCR4 axis is a potential target to improve the prognosis of ESCC on the basis of existing chemotherapy, radiotherapy, or immunotherapy.

Table 1 Clinical trials using CXCL12/CXCR4 pathway inhibitors

Description	Drug name	Indications	Study phase	Clinical trials No.
Non-peptide small molecules CXCR4 antagonists	AMD3100 (plerixafor)	FDA-approved for HSC mobilization in NHL and MM		
		Glioblastoma	1	NCT01339039
		Ewing sarcoma, neuroblastoma, brain tumours	1,2	NCT01288573
	MSX-122	Refractory metastatic or locally advanced solid tumor	1	NCT00591682
	TG-0054 (burixafor)	MM/NHL/HD HSC	2	NCT01018979
		MM/NHL/HD	2	NCT01458288
Peptide CXCR4 antagonists	BKT-140	Multiple myeloma stem cell mobilization	1,2	NCT01010880
CXCL12-based peptides	CTCE-9908	FDA-assigned for the treatment of osteosarcoma		
CXCL12-targeted agents	NOX-A12	Dosage test healthy patient for HSCT (+/– filgrastim)	1	NCT00976378 NCT01194934
Antibodies to CXCR4	Ulocuplumab (BMS936564/MDX-1338)	Acute myeloid leukemia	1	NCT01120457 NCT0135965
Nanobodies	ALX-0651	HSC mobilization, HIV	1	NCT01374503

HCS, hematopoietic stem cells; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; HD, Hodgkin disease; HSCT, HSC transplantation.

Conclusions

Overall, current data show that the CXCL12/CXCR4 axis promotes the proliferation, invasion, and metastasis of ESCC, resulting in poor patient prognosis. However, the efficacy of CXCR4 antagonists or imaging agents in ESCC has not been fully tested in clinical trials. Additional research and clinical evaluations are therefore needed to determine the benefits of CXCL12/CXCR4 antagonism and imaging agents in patients with ESCC.

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Conflicts of interest statement

No potential conflicts of interest are disclosed.

References

1. Smyth EC, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, et al. Oesophageal cancer. Nat Rev Dis Primers. 2017; 3: 17048.
2. Ohashi S, Miyamoto S, Kikuchi O, Goto T, Amanuma Y, Muto M. Recent advances from basic and clinical studies of esophageal squamous cell carcinoma. Gastroenterology. 2015; 149: 1700-15.
3. Ilson DH, van Hillegersberg R. Management of patients with adenocarcinoma or squamous cancer of the esophagus. Gastroenterology. 2018; 154: 437-51.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69: 7-34.
5. Codipilly DC, Qin Y, Dawsey SM, Kisiel J, Topazian M, Ahlquist D, et al. Screening for esophageal squamous cell carcinoma: recent advances. Gastrointest Endosc. 2018; 88: 413-26.
6. Malik S, Sharma G, Sanaka MR, Thota PN. Role of endoscopic therapy in early esophageal cancer. World J Gastroenterol. 2018; 24: 3965-73.

7. Stone MJ, Hayward JA, Huang C, Huma ZE, Sanchez J. Mechanisms of regulation of the chemokine-receptor network. Int J Mol Sci. 2017; 18: 342.

8. Nagarsheth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol. 2017; 17: 559-72.

9. Do HTT, Lee CH, Cho J. Chemokines and their receptors: multifaceted roles in cancer progression and potential value as cancer prognostic markers. Cancers (Basel). 2020; 12: 287.

10. Arimont M, Sun SL, Leurs R, Smit M, de Esch IJP, de Graaf C. Structural analysis of chemokine receptor-ligand interactions. J Med Chem. 2017; 60: 4735-79.

11. Kufareva I, Gustavsson M, Zheng Y, Stephens BS, Handel TM. What do structures tell us about chemokine receptor function and antagonism? Annu Rev Biophys. 2017; 46: 175-98.

12. Janssens R, Struyf S, Proost P. The unique structural and functional features of CXCL12. Cell Mol Immunol. 2018; 15: 299-311.

13. Ahirwar DK, Nasser MW, Ouseph MM, Elbaz M, Cuitino MC, Kladney RD, et al. Fibroblast-derived CXCL12 promotes breast cancer metastasis by facilitating tumor cell intravasation. Oncogene. 2018; 37: 4428-42.

14. Janssens R, Struyf S, Proost P. Pathological roles of the homeostatic chemokine CXCL12. Cytokine Growth Factor Rev. 2018; 44: 51-68.

15. Egawa T, Kawabata K, Kawamoto H, Amada K, Okamoto R, Fujii N, et al. The earliest stages of B cell development require a chemokine stromal cell-derived factor/Pre-B cell growth-stimulating factor. Immunity. 2001; 15: 323-34.

16. Nagasawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, et al. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. Nature. 1996; 382: 635-8.

17. Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). J Exp Med. 1996; 184: 1101-9.

18. Ratajczak MZ, Adamiak M. Membrane lipid rafts, master regulators of hematopoietic stem cell retention in bone marrow and their trafficking. Leukemia. 2015; 29: 1452-7.

19. Mandal M, Okoreeh MK, Kennedy DE, Maienschein-Cline M, Ai J, McLean KC, et al. CXCR4 signaling directs Igk recombination and the molecular mechanisms of late B lymphopoiesis. Nat Immunol. 2019; 20: 1393-403.

20. Chang AH, Raftrey BC, D'Amato G, Surya VN, Poduri A, Chen HI, et al. DACH1 stimulates shear stress-guided endothelial cell migration and coronary artery growth through the CXCL12-CXCR4 signaling axis. Genes Dev. 2017; 31: 1308-24.

21. Lu XJ, Zhu K, Shen HX, Nie L, Chen J. CXCR4s in teleosts: two paralogous chemokine receptors and their roles in hematopoietic stem/progenitor cell homeostasis. J Immunol. 2020; 204: 1225-41.

22. Goto M, Yoshida T, Yamamoto Y, Furukita Y, Inoue S, Fujiwara S, et al. CXCR4 Expression is associated with poor prognosis in patients with esophageal squamous cell carcinoma. Ann Surg Oncol. 2017; 24: 832-40.

23. Hersi HM, Raulf N, Gaken J, Folarin N, Tavassoli M. MicroRNA-9 inhibits growth and invasion of head and neck cancer cells and is a predictive biomarker of response to plerixafor, an inhibitor of its target CXCR4. Mol Oncol. 2018; 12: 2023-41.

24. Bao Y, Wang Z, Liu B, Lu X, Xiong Y, Shi J, et al. A feed-forward loop between nuclear translocation of CXCR4 and HIF-1alpha promotes renal cell carcinoma metastasis. Oncogene. 2018; 38: 881-95.

25. Sleightholm RL, Neilsen BK, Li J, Steele MM, Singh RK, Hollingsworth MA, et al. Emerging roles of the CXCL12/CXCR4 axis in pancreatic cancer progression and therapy. Pharmacol Ther. 2017; 179: 158-70.

26. Lecavalier-Barsoum M, Chaudary N, Han K, Koritzinsky M, Hill R, Milosevic M. Targeting the CXCL12/CXCR4 pathway and myeloid cells to improve radiation treatment of locally advanced cervical cancer. Int J Cancer. 2018; 143: 1017-28.

27. Nazari A, Khorramdelazad H, Hassanshahi G. Biological/pathological functions of the CXCL12/CXCR4/CXCR7 axes in the pathogenesis of bladder cancer. Int J Clin Oncol. 2017; 22: 991-1000.

28. Werner TA, Forster CM, Dizdar L, Verde PE, Raba K, Schott M, et al. CXCR4/CXCR7/CXCL12 axis promotes an invasive phenotype in medullary thyroid carcinoma. Br J Cancer. 2017; 117: 1837-45.

29. Mao TL, Fan KF, Liu CL. Targeting the CXCR4/CXCL12 axis in treating epithelial ovarian cancer. Gene Ther. 2017; 24: 621-9.

30. Barbieri F, Bajetto A, Thellung S, Würth R, Florio T. Drug design strategies focusing on the CXCR4/CXCR7/CXCL12 pathway in leukemia and lymphoma. Expert Opin Drug Discov. 2016; 11: 1093-109.

31. Daniel SK, Seo YD, Pillarisetty VG. The CXCL12-CXCR4/CXCR7 axis as a mechanism of immune resistance in gastrointestinal malignancies. Semin Cancer Biol. 2020; 65: 176-88.

32. Jin CH, Li Y, Xia J, Li Y, Chen M, Hu Z, et al. CXCR4 blockade improves leukemia eradication by allogeneic lymphocyte infusion. Am J Hematol. 2018; 93: 786-93.

33. Sledge GW. Targeting CXCR4-induced desmoplasia to improve checkpoint inhibition in breast cancer. Proc Natl Acad Sci U S A. 2019; 116: 4769-71.

34. Guo F, Wang Y, Liu J, Mok SC, Xue F, Zhang W. CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. Oncogene. 2016; 35: 816-26.

35. McConnell AT, Ellis R, Pathy B, Plummer R, Lovat PE, O'Boyle G. The prognostic significance and impact of the CXCR4-CXCR7-CXCL12 axis in primary cutaneous melanoma. Br J Dermatol. 2016; 175: 1210-20.

36. Kinoshita H, Yashiro M, Fukuoka T, Hasegawa T, Morisaki T, Kasashima H, et al. Diffuse-type gastric cancer cells switch their driver pathways from FGFR2 signaling to SDF1/CXCR4 axis in hypoxic tumor microenvironments. Carcinogenesis. 2015; 36: 1511-20.

37. Wald O. CXCR4 based therapeutics for non-small cell lung cancer (NSCLC). J Clin Med. 2018; 7: 303.

38. Ozawa PM, Ariza CB, Ishibashi CM, Fujita TC, Banin-Hirata BK, Oda JM, et al. Role of CXCL12 and CXCR4 in normal cerebellar development and medulloblastoma. Int J Cancer. 2016; 138: 10-3.

39. Chen IX, Chauhan VP, Posada J, Ng MR, Wu MW, Adstamongkonkul P, et al. Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. Proc Natl Acad Sci U S A. 2019; 116: 4558-66.

40. Tian X, Xie G, Xiao H, Ding F, Bao W, Zhang M. CXCR4 knockdown prevents inflammatory cytokine expression in macrophages by suppressing activation of MAPK and NF-kappaB signaling pathways. Cell Biosci. 2019; 9: 55.

41. Tsou LK, Huang YH, Song JS, Ke YY, Huang JK, Shia KS. Harnessing CXCR4 antagonists in stem cell mobilization, HIV infection, ischemic diseases, and oncology. Med Res Rev. 2018; 38: 1188-234.

42. Zhou W, Guo S, Liu M, Burow ME, Wang G. Targeting CXCL12/CXCR4 axis in tumor immunotherapy. Curr Med Chem. 2019; 26: 3026-41.

43. Li Z, Wang Y, Shen Y, Qian C, Oupicky D, Sun M. Targeting pulmonary tumor microenvironment with CXCR4-inhibiting nanocomplex to enhance anti-PD-L1 Immunotherapy. Sci Adv. 2020; 6: eaaz9240.

44. Meng W, Xue S, Chen Y. The role of CXCL12 in tumor microenvironment. Gene. 2018; 641: 105-10.

45. Ziegler ME, Hatch MM, Wu N, Muawad SA, Hughes CC. mTORC2 mediates CXCL12-induced angiogenesis. Angiogenesis. 2016; 19: 359-71.

46. Yin X, Liu Z, Zhu P, Wang Y, Ren Q, Chen H, et al. CXCL12/CXCR4 promotes proliferation, migration, and invasion of adamantinomatous craniopharyngiomas via PI3K/AKT signal pathway. J Cell Biochem. 2018; 120: 9724-36.

47. Lu C, Xu F, Gu J, Yuan Y, Zhao G, Yu X, et al. Clinical and biological significance of stem-like CD133(+)CXCR4(+) cells in esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2015; 150: 386-95.

48. Zhang SS, Han ZP, Jing YY, Tao SF, Li TJ, Wang H, et al. CD133(+)CXCR4(+) colon cancer cells exhibit metastatic potential and predict poor prognosis of patients. BMC Med. 2012; 10: 85.

49. Zhang S, Wang Y, Chen M, Sun L, Han J, Elena VK, et al. CXCL12 methylation-mediated epigenetic regulation of gene expression in papillary thyroid carcinoma. Sci Rep. 2017; 7: 44033.

50. Zhi Y, Chen J, Zhang S, Chang X, Ma J, Dai D. Down-Regulation of CXCL12 by DNA hypermethylation and its involvement in gastric cancer metastatic progression. Dig Dis Sci. 2011; 57: 650-9.

51. Li B, Wang Z, Wu H, Xue M, Lin P, Wang S, et al. Epigenetic Regulation of CXCL12 plays a critical role in mediating tumor progression and the immune response in osteosarcoma. Cancer Res. 2018; 78: 3938-53.

52. Mori T, Kim J, Yamano T, Takeuchi H, Huang S, Umetani N, et al. Epigenetic up-regulation of C-C chemokine receptor 7 and C-X-C chemokine receptor 4 expression in melanoma cells. Cancer Res. 2005; 65: 1800-7.

53. Ma X, Shang F, Zhu W, Lin Q. CXCR4 expression varies significantly among different subtypes of glioblastoma multiforme (GBM) and its low expression or hypermethylation might predict favorable overall survival. Expert Rev Neurother. 2017; 17: 941-6.

54. Lopez-Haber C, Barrio-Real L, Casado-Medrano V, Kazanietz MG. Heregulin/ErbB3 signaling enhances CXCR4-Driven Rac1 activation and breast cancer cell motility via hypoxia-inducible factor 1alpha. Mol Cell Biol. 2016; 36: 2011-26.

55. Garg B, Giri B, Modi S, Sethi V, Castro I, Umland O, et al. NFkappaB in pancreatic stellate cells reduces infiltration of tumors by cytotoxic T cells and killing of cancer cells, via up-regulation of CXCL12. Gastroenterology. 2018; 155: 880-91.

56. García-Irigoyen O, Latasa MU, Carotti S, Uriarte I, Elizalde M, Urtasun R, et al. Matrix metalloproteinase 10 contributes to hepatocarcinogenesis in a novel crosstalk with the stromal derived factor 1/C-X-C chemokine receptor 4 axis. Hepatology. 2015; 62: 166-78.

57. Conley-LaComb MK, Saliganan A, Kandagatla P, Chen YQ, Cher ML, Chinni SR. PTEN loss mediated Akt activation promotes prostate tumor growth and metastasis via CXCL12/CXCR4 signaling. Mol Cancer. 2013; 12: 85.

58. Gao P, Wange RL, Zhang N, Oppenheim JJ, Howard OM. Negative regulation of CXCR4-mediated chemotaxis by the lipid phosphatase activity of tumor suppressor PTEN. Blood. 2005; 106: 2619-26.

59. Yu PF, Huang Y, Xu CL, Lin LY, Han YY, Sun WH, et al. Downregulation of CXCL12 in mesenchymal stromal cells by TGFbeta promotes breast cancer metastasis. Oncogene. 2017; 36: 840-9.

60. Yang J, Zhang L, Jiang Z, Ge C, Zhao F, Jiang J, et al. TCF12 promotes the tumorigenesis and metastasis of hepatocellular carcinoma via upregulation of CXCR4 expression. Theranostics. 2019; 9: 5810-27.

61. Salcedo R, Wasserman K, Young HA, Grimm MC, Howard OM, Anver MR, et al. Vascular endothelial growth factor and basic fibroblast growth factor induce expression of CXCR4 on human endothelial cells: in vivo neovascularization induced by stromal-derived factor-1alpha. Am J Pathol. 1999; 154: 1125-35.

62. Gebert LFR, MacRae IJ. Regulation of microRNA function in animals. Nat Rev Mol Cell Biol. 2019; 20: 21-37.

63. Givel AM, Kieffer Y, Scholer-Dahirel A, Sirven P, Cardon M, Pelon F, et al. miR200-regulated CXCL12beta promotes fibroblast heterogeneity and immunosuppression in ovarian cancers. Nat Commun. 2018; 9: 1056.

64. Liu H, Liu Y, Liu W, Zhang W, Xu J. EZH2-mediated loss of miR-622 determines CXCR4 activation in hepatocellular carcinoma. Nat Commun. 2015; 6: 8494.

65. Wei CY, Zhu MX, Lu NH, Liu JQ, Yang YW, Zhang Y, et al. Circular RNA circ_0020710 drives tumor progression and immune evasion by regulating the miR-370-3p/CXCL12 axis in melanoma. Mol Cancer. 2020; 19: 84.

66. Li G, An J, Han X, Zhang X, Wang W, Wang S. Hypermethylation of microRNA-149 activates SDF-1/CXCR4 to promote osteogenic differentiation of mesenchymal stem cells. J Cell Physiol. 2019; 234: 23485-94.

67. Zhang J, Liu J, Liu Y, Wu W, Li X, Wu Y, et al. miR-101 represses lung cancer by inhibiting interaction of fibroblasts and cancer cells by down-regulating CXCL12. Biomed Pharmacother. 2015; 74: 215-21.

68. Scala S. Molecular pathways: targeting the CXCR4-CXCL12 axis–untapped potential in the tumor microenvironment. Clin Cancer Res. 2015; 21: 4278-85.

69. Li M, Sun X, Ma L, Jin L, Zhang W, Xiao M, et al. SDF-1/CXCR4 axis induces human dental pulp stem cell migration through FAK/PI3K/Akt and GSK3beta/beta-catenin pathways. Sci Rep. 2017; 7: 40161.

70. O'Hayre M, Degese MS, Gutkind JS. Novel insights into G protein and G protein-coupled receptor signaling in cancer. Curr Opin Cell Biol. 2014; 27: 126-35.

71. Tian Y, Yin H, Deng X, Tang B, Ren X, Jiang T. CXCL12 induces migration of oligodendrocyte precursor cells through the CXCR4-activated MEK/ERK and PI3K/AKT pathways. Mol Med Rep. 2018; 18: 4374-80.

72. Lu Y, Xing J, Yin X, Zhu X, Yang A, Luo J, et al. Bone marrow-derived CD44(+) cells migrate to tissue-engineered constructs via SDF-1/CXCR4-JNK pathway and aid bone repair. Stem Cells Int. 2019; 2019: 1513526.

73. Lan TH, Xu DP, Huang MT, Song JX, Wu HL, Li M. Ginsenoside Rb1 prevents homocysteine-induced EPC dysfunction via VEGF/p38MAPK and SDF-1/CXCR4 activation. Sci Rep. 2017; 7: 13061.

74. Liu Y, Feng Q, Miao J, Wu Q, Zhou S, Shen W, et al. C-X-C motif chemokine receptor 4 aggravates renal fibrosis through activating JAK/STAT/GSK3beta/beta-catenin pathway. J Cell Mol Med. 2020; 24: 3837-55.

75. Pozzobon T, Goldoni G, Viola A, Molon B. CXCR4 signaling in health and disease. Immunol Lett. 2016; 177: 6-15.

76. Cheng ZJ, Zhao J, Sun Y, Hu W, Wu YL, Cen B, et al. beta-arrestin differentially regulates the chemokine receptor CXCR4-mediated signaling and receptor internalization, and this implicates multiple interaction sites between beta-arrestin and CXCR4. J Biol Chem. 2000; 275: 2479-85.

77. Luker KE, Lewin SA, Mihalko LA, Schmidt BT, Winkler JS, Coggins NL, et al. Scavenging of CXCL12 by CXCR7 promotes tumor growth and metastasis of CXCR4-positive breast cancer cells. Oncogene. 2012; 31: 4750-8.

78. Lin L, Han MM, Wang F, Xu LL, Yu HX, Yang PY. CXCR7 stimulates MAPK signaling to regulate hepatocellular carcinoma progression. Cell Death Dis. 2014; 5: e1488.

79. Song ZY, Wang F, Cui SX, Gao ZH, Qu XJ. CXCR7/CXCR4 heterodimer-induced histone demethylation: a new mechanism of colorectal tumorigenesis. Oncogene. 2019; 38: 1560-75.

80. Décaillot FM, Kazmi MA, Lin Y, Ray-Saha S, Sakmar TP, Sachdev P. CXCR7/CXCR4 heterodimer constitutively recruits beta-arrestin to enhance cell migration. J Biol Chem. 2011; 286: 32188-97.

81. Guo J, Yu X, Gu J, Lin Z, Zhao G, Xu F, et al. Regulation of CXCR4/AKT-signaling-induced cell invasion and tumor metastasis by RhoA, Rac-1, and Cdc42 in human esophageal cancer. Tumour Biol. 2016; 37: 6371-8.

82. Uchi Y, Takeuchi H, Matsuda S, Saikawa Y, Kawakubo H, Wada N, et al. CXCL12 expression promotes esophageal squamous cell carcinoma proliferation and worsens the prognosis. BMC Cancer. 2016; 16: 514.

83. Sasaki K, Natsugoe S, Ishigami S, Matsumoto M, Okumura H, Setoyama T, et al. Expression of CXCL12 and its receptor CXCR4 in esophageal squamous cell carcinoma. Oncol Rep. 2009; 21: 65-71.

84. Jiang Q, Sun Y, Liu X. CXCR4 as a prognostic biomarker in gastrointestinal cancer: a meta-analysis. Biomarkers. 2019; 24: 510-6.

85. Kaifi JT, Yekebas EF, Schurr P, Obonyo D, Wachowiak R, Busch P, et al. Tumor-cell homing to lymph nodes and bone marrow and CXCR4 expression in esophageal cancer. J Natl Cancer Inst. 2005; 97: 1840-7.

86. Lu CL, Guo J, Gu J, Ge D, Hou YY, Lin ZW, et al. CXCR4 heterogeneous expression in esophageal squamous cell cancer and stronger metastatic potential with CXCR4-positive cancer cells. Dis Esophagus. 2014; 27: 294-302.

87. Łukaszewicz-Zając M, Mroczko B, Kozłowski M, Szmitkowski M. The serum concentrations of chemokine CXCL12 and its specific receptor CXCR4 in patients with esophageal cancer. Dis Markers. 2016; 2016: 7963895.

88. Janowski M. Functional diversity of SDF-1 splicing variants. Cell Adh Migr. 2009; 3: 243-9.

89. Kucia M, Jankowski K, Reca R, Wysoczynski M, Bandura L, Allendorf DJ, et al. CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion. J Mol Histol. 2004; 35: 233-45.

90. Yang X, Lu Q, Xu Y, Liu C, Sun Q. Clinicopathologic significance of CXCR4 expressions in patients with esophageal squamous cell carcinoma. Pathol Res Pract. 2020; 216: 152787.

91. Wang DF, Lou N, Qiu MZ, Lin YB, Liang Y. Effects of CXCR4 gene silencing by lentivirus shRNA on proliferation of the EC9706 human esophageal carcinoma cell line. Tumour Biol. 2013; 34: 2951-9.

92. Zhuo W, Jia L, Song N, Lu XA, Ding Y, Wang X, et al. The CXCL12-CXCR4 chemokine pathway: a novel axis regulates lymphangiogenesis. Clin Cancer Res. 2012; 18: 5387-98.

93. Chen YH, Li SH, Lu HI, Lo CM. Prognostic value of SDF-1alpha expression in patients with esophageal squamous cell carcinoma receiving esophagectomy. Cancers (Basel). 2020; 12: 1067.

94. Kryczek I, Lange A, Mottram P, Alvarez X, Cheng P, Hogan M, et al. CXCL12 and vascular endothelial growth factor synergistically induce neoangiogenesis in human ovarian cancers. Cancer Res. 2005; 65: 465-72.

95. Lim RZL, Li L, Yong EL, Chew N. STAT-3 regulation of CXCR4 is necessary for the prenylflavonoid Icaritin to enhance mesenchymal stem cell proliferation, migration and osteogenic differentiation. Biochim Biophys Acta Gen Subj. 2018; 1862: 1680-92.

96. Jeong YM, Cheng XW, Lee S, Lee KH, Cho H, Kang JH, et al. Preconditioning with far-infrared irradiation enhances proliferation, cell survival, and migration of rat bone marrow-derived stem cells via CXCR4-ERK pathways. Sci Rep. 2017; 7: 13718.

97. Zou W, Machelon V, Coulomb-L'Hermin A, Borvak J, Nome F, Isaeva T, et al. Stromal-derived factor-1 in human tumors recruits and alters the function of plasmacytoid precursor dendritic cells. Nat Med. 2001; 7: 1339-46.

98. Zhao E, Wang L, Dai J, Kryczek I, Wei S, Vatan L, et al. Regulatory T cells in the bone marrow microenvironment in patients with prostate cancer. Oncoimmunology. 2012; 1: 152-61.

99. Eckert F, Schilbach K, Klumpp L, Bardoscia L, Sezgin EC, Schwab M, et al. Potential role of CXCR4 targeting in the context of radiotherapy and immunotherapy of cancer. Front Immunol. 2018; 9: 3018.

100. Gockel I, Schimanski CC, Heinrich C, Wehler T, Frerichs K, Drescher D, et al. Expression of chemokine receptor CXCR4 in esophageal squamous cell and adenocarcinoma. BMC Cancer. 2006; 6: 290.

101. Wu J, Wu X, Liang W, Chen C, Zheng L, An H. Clinicopathological and prognostic significance of chemokine receptor CXCR4 overexpression in patients with esophageal cancer: a meta-analysis. Tumour Biol. 2014; 35: 3709-15.

102. Yue D, Zhang D, Shi X, Liu S, Li A, Wang D, et al. Chloroquine inhibits stemness of esophageal squamous cell carcinoma cells through targeting CXCR4-STAT3 pathway. Front Oncol. 2020; 10: 311.

103. De Clercq E. The bicyclam AMD3100 story. Nat Rev Drug Discov. 2003; 2: 581-7.

104. Wang J, Tannous BA, Poznansky MC, Chen H. CXCR4 antagonist AMD3100 (plerixafor): from an impurity to a therapeutic agent. Pharmacol Res. 2020; 159: 105010.

105. De Clercq E. Recent advances on the use of the CXCR4 antagonist plerixafor (AMD3100, Mozobil) and potential of other CXCR4 antagonists as stem cell mobilizers. Pharmacol Ther. 2010; 128: 509-18.

106. DiPersio JF, Micallef IN, Stiff PJ, Bolwell BJ, Maziarz RT, Jacobsen E, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol. 2009; 27: 4767-73.

107. Kim SY, Lee CH, Midura BV, Yeung C, Mendoza A, Hong SH, et al. Inhibition of the CXCR4/CXCL12 chemokine pathway reduces the development of murine pulmonary metastases. Clin Exp Metastasis. 2008; 25: 201-11.

108. Vater A, Sahlmann J, Kröger N, Zöllner S, Lioznov M, Maasch C, et al. Hematopoietic stem and progenitor cell mobilization in mice and humans by a first-in-class mirror-image oligonucleotide inhibitor of CXCL12. Clin Pharmacol Ther. 2013; 94: 150-7.

109. Steurer M, Montillo M, Scarfò L, Mauro FR, Andel J, Wildner S, et al. Olaptesed pegol (NOX-A12) with bendamustine and rituximab: a phase IIa study in patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica. 2019; 104: 2053-60.

110. Ludwig H, Weisel K, Petrucci MT, Leleu X, Cafro AM, Garderet L, et al. Olaptesed pegol, an anti-CXCL12/SDF-1 Spiegelmer, alone and with bortezomib-dexamethasone in relapsed/refractory multiple myeloma: a Phase IIa study. Leukemia. 2017; 31: 997-1000.

111. Nimmagadda S, Pullambhatla M, Pomper MG. Immunoimaging of CXCR4 expression in brain tumor xenografts using SPECT/CT. J Nucl Med. 2009; 50: 1124-30.

112. Hanaoka H, Mukai T, Tamamura H, Mori T, Ishino S, Ogawa K, et al. Development of a 111In-labeled peptide derivative targeting a chemokine receptor, CXCR4, for imaging tumors. Nucl Med Biol. 2006; 33: 489-94.

113. Jacobson O, Weiss ID, Szajek L, Farber JM, Kiesewetter DO. 64Cu-AMD3100—a novel imaging agent for targeting chemokine receptor CXCR4. Bioorg Med Chem. 2009; 17: 1486-93.

114. Luker K, Gupta M, Luker G. Bioluminescent CXCL12 fusion protein for cellular studies of CXCR4 and CXCR7. Biotechniques. 2009; 47: 625-32.

115. Meincke M, Tiwari S, Hattermann K, Kalthoff H, Mentlein R. Near-infrared molecular imaging of tumors via chemokine receptors CXCR4 and CXCR7. Clin Exp Metastasis. 2011; 28: 713-20.

116. Brickute D, Braga M, Kaliszczak MA, Barnes C, Lau D, Carroll L, et al. Development and evaluation of an (18)F-radiolabeled monocyclam derivative for imaging CXCR4 expression. Mol Pharm. 2019; 16: 2106-17.

117. Koishi K, Yoshikawa R, Tsujimura T, Hashimoto-Tamaoki T, Kojima S, Yanagi H, et al. Persistent CXCR4 expression after preoperative chemoradiotherapy predicts early recurrence and poor prognosis in esophageal cancer. World J Gastroenterol. 2006; 12: 7585-90.

118. Meng J, Ge Y, Xing H, Wei H, Xu S, Liu J, et al. Synthetic CXCR4 antagonistic peptide assembling with nanoscaled micelles combat acute myeloid leukemia. Small. 2020; 16: e2001890.

119. Wang S, Chen C, Li J, Xu X, Chen W, Li F. The CXCL12/CXCR4 axis confers temozolomide resistance to human glioblastoma cells via up-regulation of FOXM1. J Neurol Sci. 2020; 414: 116837.

120. Li B, Zeng Y, Reeves PM, Ran C, Liu Q, Qu X, et al. AMD3100 augments the efficacy of mesothelin-targeted, immune-activating VIC-008 in mesothelioma by modulating intratumoral immunosuppression. Cancer Immunol Res. 2018; 6: 539-51.

121. Chen Y, Ramjiawan RR, Reiberger T, Ng MR, Hato T, Huang Y, et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. Hepatology. 2015; 61: 1591-602.