REVIEW

CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks

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Increasing evidence indicates that the tumor microenvironment has critical roles in all aspects of cancer biology, including growth, angiogenesis, metastasis and progression. Although chemokines and their receptors were originally identified as mediators of inflammatory diseases, it is being increasingly recognized that they serve as critical communication bridges between tumor cells and stromal cells to create a permissive microenvironment for tumor growth and metastasis. Thus, an important therapeutic strategy for cancer is to break this communication channel and isolate tumor cells for long-term elimination. Cytokine CXCL12 (also known as stromal-derived factor 1 α) and its receptor CXCR4 represent the most promising actionable targets for this strategy. Both are overexpressed in various cancer types, and this aberrant expression strongly promotes proliferation, migration and invasion through multiple signal pathways. Several molecules that target CXCL12 or CXCR4 have been developed to interfere with tumor growth and metastasis. In this article, we review our current understanding of the CXCL12/CXCR4 axis in cancer tumorigenesis and progression and discuss its therapeutic implications.

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INTRODUCTION

Cancer is a major public health problem in the United States and many other parts of the world. One in four deaths in the United States is due to cancer.¹ The high death rate from cancer is mainly due to metastasis and relapse and a lack of effective therapies. Increasing evidence indicates that tumor–stromal cell interactions have a crucial role in tumor initiation and progression.² CXCL12 and its receptors, CXCR4 and CXCR7, are the key factors in the link between cancer cells and their microenvironment. CXCL12 expression is associated with patient survival, on the basis of a recent meta-analysis of microarray data on 2970 patients from 23 studies.³ Another study found that CXCL12 was the most significant predictor of disease-free survival on the basis of the expression of ~17 000 genes and 341 micro RNAs in 2129 ovarian cancer samples.⁴ Thus, CXCL12 may have an important role in cancer progression. This review focuses on the pathologic role of CXCL12/CXCR4/CXCR7 in cancer and the therapeutic implication of targeting this axis in cancer treatment.

THE CXCL12/CXCR4 AXIS

CXCL12, also known as stromal-derived factor 1 α , is one of the most important CXC chemokines; it is vital to normal B cell growth and cardiac tissue initiation. The *CXCL12* gene is located at 10q11.1 and has 6 exons. There are three GC boxes (–451 to –446, –87 to –82 and –63 to –58) and one CAAT box (–423 to –419) on the promoter of the gene that are binding sites for transcription factors SP1 and CTF, respectively.⁵ CXCL12 has 68 amino acids and its molecular weight is 8 kDa. CXCL12 is

expressed widely in multiple normal tissues and serum; it is also expressed by multiple immune cells, endothelial cells, cancer cells, stromal fibroblasts and stem cells.⁶ CXCL12 acts by binding to the seven-transmembrane G-protein-coupled receptor CXCR4. The interactions between CXCL12 and CXCR4 comprise a biological axis that affects the growth, angiogenesis and metastasis of cancer.

The *CXCR4* gene is located at 2q21 and has two exons with 103 nucleotides (nt) and 1564 nt, respectively. CXCR4 has 352 amino acids and its molecular weight is 48 kDa. CXCR4 is expressed on multiple cell types, including lymphocytes, hematopoietic stem cells, endothelial cells, epithelial cells, cancer cells and stromal fibroblasts.⁷ The mutation of the *CXCR4* gene was reported in several cancer types, such as pituitary tumor⁸ and familial chronic lymphocytic leukemia (CLL).⁹ Mutation of the *CXCR4* gene was also reported in the fourth transmembrane region of CXCR4 in one colon cancer cell line and one melanoma cell line.¹⁰ Amplification of the *CXCR4* gene locus was suggested to be an early event in the development of high-grade serous ovarian cancer.¹¹

CXCL12 may also activate CXCR7. CXCR7, a seven-transmembrane G-protein-coupled receptor, can bind to CXCL12 with even greater affinity than can the CXCR4 receptor.¹² CXCR7 is expressed in various normal tissues, and its expression seems to be enhanced during pathological inflammation and tumor development.¹³ A new study has proposed that CXCR7 is overexpressed in tumor cells and tumor endothelial cells.¹⁴ Meanwhile, CXCR7 promotes cell proliferation, angiogenesis and invasion, inducing the development and progression of cancer.¹⁵

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CXCL12/CXCR4/CXCR7 EXPRESSION IN CANCER

The level of CXCL12/CXCR4 is increased in many types of cancer, such as breast cancer,¹⁶ gastric cancer,¹⁷ pancreatic cancer,^{18,19} ovarian carcinoma,^{20,21} cervical carcinoma²² and oral squamous cell carcinoma.²³ Cytokine-expression profiles from CLL patients' serum revealed that three gene products, including CXCL12, were upregulated in the high stage (Rai stage III/IV) compared with low stage (Rai stage 0/I/II).²⁴ Furthermore, CXCL12/CXCR4 expression is correlated with metastasis and prognosis. High expression of CXCR4 and CXCL12 was found to be significantly correlated with liver and lymphatic metastases¹⁷ and low overall and disease-free survival rates.^{18,20,25} Thus, CXCL12/CXCR4 may serve as an independent predictor of poor survival in cancer patients.^{26–29}

Recently, it was reported that CXCL12 combined with a set of other genes may serve as good prognostic biomarkers or diagnostic markers for cancers. For example, Sanz-Pamplona *et al.*³⁰ have identified four organ-specific protein–protein interaction networks including organ-specific proteins that exert a range of functions allowing cell survival and growth of distant organs in human breast cancer metastases on the basis of a network-based approach. Three of these selected proteins (CXCL12, DSC2 and TFDP2) were associated with metastasis to specific organs. A recent study reported that combination of serum CXCL5, CXCL12 and carcinoembryonic antigen achieved 92.8% specificity at 75.0% sensitivity to predict distant metastasis of gastric cancer.³¹ In acute lymphoblastic leukemia (ALL), combination of genetic polymorphisms in the 3'-untranslated repeat (UTR) region of the CXCL12 (rs1801157) and TP53 codon 72 (rs1042522) genes may serve as susceptibility markers for ALL disease.³² Low CCL27/CCR10 and CXCL12/CXCR4 intratumoral mRNA ratios were suggested to be robust predictive factors for the development of distant metastases in primary cutaneous melanoma.³³ Thus, combination of CXCL12 with some other genes may serve as better prognostic biomarkers than itself alone.

In several studies, CXCL12 expression differed in different subtypes of cancer. For example, lower expression of CXCL12 in tumor cells was seen in patients with ovarian clear cell carcinoma ($n=28$) than was seen in those with high-grade serous carcinoma ($n=108$).³⁴ Meanwhile, patients with undifferentiated carcinoma had significantly higher plasma CXCL12 levels than did patients with serous cystadenocarcinoma.²⁸ However, in another study, elevated levels of blood CXCL12 were found in ovarian cancer, independent of the cancer type (18 serous carcinoma, four endometrioid carcinoma, three mucinous carcinoma and two macrocellular carcinoma).³⁵ This controversial finding may have been due to the small number of ovarian cancer cases. Nevertheless, serum CXCL12 levels may be affected by multiple cell types (for example, immune cells).

CXCR4 is overexpressed in more than 23 human cancers.³⁶ Although CXCR4 is a membrane receptor, many studies have found that tumor cells express nuclear, cytoplasmic and membrane CXCR4 staining.²⁹ This phenomenon may be due to CXCR4 activation by CXCL12, which induces CXCR4 internalization and specific downstream signals and leads to CXCR4 translocation from the membrane to the cytoplasm. Some recent studies have demonstrated that different expression patterns of CXCR4 by cancer cells indicate differences in the biological behavior of cancer. High expression of CXCR4 in the cytoplasm or cytomembrane of tumor cells indicates a poor prognosis, whereas high expression in the nucleus indicates a better prognosis. CXCR4 was found to be present in the cytoplasm and nuclei of tumor cells in breast cancer, and only cytoplasmic expression was associated with lymph node metastasis;¹⁶ these findings bear some similarities to those of Su *et al.*³⁷ Wagner PL³⁸ *et al.* discovered that cytomembrane expression of CXCR4 in lung adenocarcinoma is an independent risk factor that is associated with poor disease-free survival, whereas nuclear expression confers a survival

benefit. Thus, CXCR4 may promote tumor cell proliferation and metastasis when present in the cytoplasm or cell membrane, but is prevented from exerting these effects when it is localized in the nucleus. This observation may be due to CXCR4, maintaining a close physical association with extracellular signal-regulated kinases (ERKs) and cyclophilin A in the vicinity of the nuclear membrane, which induce the phosphorylation and nuclear translocation of ERK1/2.³⁸

CXCR7 was demonstrated to be a new factor in the CXCL12/CXCR4 axis, binding to CXCL12 with even greater affinity than CXCR4. CXCR7 was found to be overexpressed in various tumor cells, including breast, prostate, ovarian and lung cancer.^{39,40} By binding to CXCL12, CXCR7 promotes cancer growth, angiogenesis and progression.

REGULATION OF CXCL12/CXCR4/CXCR7 IN CANCER

CXCL12/CXCR4 can be regulated by epigenetic, transcriptional and post-transcriptional factors. The regulation of CXCL12/CXCR4 expression by promoter hypermethylation is common in cancer. Recent studies have demonstrated that the CXCL12 gene modulates metastatic potential in cancer, where it controls its own regulation in an autocrine loop. Epigenetic silencing causes the loss of autocrine expression and results in an imbalance in the expression of CXCL12/CXCR4. Cancer cells that lack expression of CXCL12 but maintain overexpression of CXCR4 can selectively spread to target organs in which CXCL12 is highly secreted.⁴¹ CXCL12-promoter hypermethylation has been detected in cancer and contributes to its metastatic potential.^{41–43} Loss of DNA methylation in the CXCR4 promoter was detected in various types of cancer, including breast cancer,⁴⁴ leading to the upregulation of CXCR4. Studies revealed that overexpression of CXCR4 was significantly related to the lymph node metastasis status, whereas decreased expression of CXCL12 mRNA was significantly associated with positive lymph node metastasis,⁴¹ demonstrating that low CXCL12 levels in cancer cells contribute to their metastatic potential. In addition, tamoxifen, similar to 5-dAzaC, led to increased levels of CXCL12 in MCF-7 breast cancer cells by reducing the methylation of the CXCL12 promoter.⁴⁵

CXCL12/CXCR4 can be regulated by many factors, such as transforming growth factor- β ^{1,46} tumor necrosis factor- α ,^{47,48} estradiol and C-myc. Recent studies have reported that estradiol can mediate the transcriptional regulation of CXCL12, CXCR4 and CXCR7. Estradiol enhanced the expression of both CXCL12 and CXCR4 but repressed the expression of CXCR7 in breast cancer cells.^{49,50} Transcriptional factors such as c-myc,⁵¹ snail family zinc finger 2, SNAI2 (SLUG)⁵² and Akt1^(ref. 53) can elevate CXCR4 and CXCL12 expression in cancer cells. In addition, increased hypoxia-inducible factor-2 can bind to the CXCL12 promoter under hypoxic conditions, increasing CXCL12 expression.⁵⁴ P53 inhibits the expression of CXCL12 in cancers.^{55–57} FOXP3 overexpression in breast cancer cells significantly decreases the expression of CXCR4.⁵⁸

Several recent studies revealed other regulating molecules in cancers, such as lysophosphatidic acid.⁵⁹ Lysophosphatidic acid can upregulate CXCL12/CXCR4 axis expression, leading to an increased invasiveness of ovarian cancer.⁶⁰ In addition, lysophosphatidic acid increases CXCL12 expression by activating the autocrine transforming growth factor- β 1-Smad signaling pathway in human adipose tissue-derived mesenchymal stem cells.⁵⁹

CD164 is a type I integral transmembrane sialomucin that has been reported to have a role in the proliferation, adhesion and differentiation of hematopoietic stem cells.^{61,62} A recent study reported that CD164 promotes HCT116 colon cancer cell proliferation and metastasis by regulating the CXCR4 signaling pathway.⁶³ In ovarian cancer, CD164 in the nucleus can induce activation of the CXCR4 promoter,⁶⁴ increasing the amounts of CXCR4 and CXCL12 (Figure 1).

Figure 1. Regulatory network of CXCL12/CXCR4. CXCL12/CXCR4 expression can be regulated by methylation, enhancers, many signaling factors and post-transcriptional mechanisms, such as microRNAs (miRNAs).

HOXA9 is a DNA-binding transcription factor that may regulate gene expression, differentiation and morphogenesis. The expression of HOXA9 in epithelial ovarian cancer cells induced the transcriptional activation of transforming growth factor- β 2, which acted in a paracrine manner on fibroblasts to induce CXCL12 expression.⁶⁵

CD40 is a co-stimulatory molecule found on antigen-presenting cells that is required for their activation. CD24 is a glycoprotein expressed at the surface of B lymphocytes and differentiating neuroblasts. Recent studies reported that CD40^(ref. 66) and CD24^(ref. 67) can upregulate CXCR4, inducing ovarian cancer cell migration. In addition, Prostaglandin E (2)^(ref. 68) and interleukin (IL)-2^(ref. 69) can induce CXCR4 expression in stromal cells such as cancer-associated myeloid-derived suppressor cells and CD4 (+) CD25 (+) FOXP3 (+) regulatory T cells, leading to the migration of these cells toward the chemokine CXCL12 in the tumor microenvironment.

Recently, researchers found that CXCL12/CXCR4 can be regulated by post-transcriptional mechanisms, including micro RNAs in various tumors. CXCL12 expression in cancer cells is targeted by many microRNAs, such as miR-1,⁷⁰ miR-126,^{71,72} miR-140,⁷³ miR-141,⁷⁴ miR-146a-5p,⁷⁵ miR-27a and miR-27b,⁷⁶ miR-430⁷⁷ and miR-886-3p.⁷⁸ CXCR4 can be regulated by miR-1,⁷⁰ miR-9,^{79,80} miR-126,⁸¹ miR-146a,⁸² miR-150,⁸³ miR-199-5p,⁸⁴ miR-494-3p,⁸⁵ miR-133b,⁸⁶ miR-139⁸⁷ and miR-224.⁸⁸ Moreover, miR-200a can increase CXCR4 expression in cancer cells.⁸⁹ CXCR7 can be regulated by miR-430.⁷⁷ The microRNAs that target CXCL12/CXCR4/CXCR7 may suppress cancer development and progression (Figure 1). On the basis of tests in breast cancer patients, miR-146a was recently patented as a CXCR4 antagonist by the Italian Ministry of Health.⁹⁰

EFFECTS OF CXCL12/CXCR4 ON CANCER AND ITS MECHANISM

CXCL12 affects cancer biology mainly via the following two mechanisms: (a) by direct autocrine effects that promote cancer cell growth, metastasis and angiogenesis and (b) by indirect effects, including the recruitment of CXCR4-expressing cancer cells to CXCL12-expressing organs or CXCR4-positive stromal cells to tumor sites.³⁹ CXCL12 functions as a growth and survival factor and as a pro-angiogenic factor for cancer cell growth. It can attract CXCR4-expressing cancer cells to distant organs to initiate metastasis.

Figure 2. CXCL12/CXCR4/CXCR7 signaling pathway. CXCL12/CXCR4 and CXCL12/CXCR7 suppress apoptosis and promote proliferation, angiogenesis and metastasis in tumors by targeting multiple signaling pathways and transcription factors.

CXCL12/CXCR4 can stimulate diversified signal transduction pathways and their effect molecules; enhance the proliferation and migration of tumor cells; induce angiogenesis in tumor tissues; and promote cancer infiltration and metastasis (Figure 2).

THE CXCL12/CXCR4 AXIS PROMOTES PROLIFERATION, INHIBITS APOPTOSIS AND DRIVES TUMOR GROWTH

Recent studies have revealed that CXCL12/CXCR4 promotes tumorigenesis in cancer, such as ovarian cancer. Ovarian cancer is a complex disease that develops from multiple extraovarian origins. Granulosa cells secrete CXCL12 as a key factor that can attract and maintain malignant cells in the ovaries and promote tumorigenesis.⁹¹ Epithelial cells from the surface of the ovaries and fallopian tubes were found to stain positive for CXCL12, whereas the follicles within the ovary did not, indicating that epithelial ovarian cancer originates from either of these epithelia.⁹² Therefore, CXCL12/CXCR4 may have an important role in the tumorigenesis of ovarian cancer.

It is known that CXCL12 activates distinct signaling pathways, such as epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MAPK), PI3K/AKT, Wnt pathway and NF- κ B to mediate cancer cell growth, migration and invasion¹⁹ (Figure 2). CXCL12 can promote the proliferation,^{93,94} migration and invasion of ovarian cancer cells.^{60,64,95,96} CXCL12/CXCR4 activation induces EGFR phosphorylation and the activation of extracellular signal-regulated kinases (ERK1/2) and Akt.^{93,94} These results suggest that 'cross-talk' exists between the CXCL12/CXCR4 and EGFR intracellular pathways that link cell proliferation signals in cancer.⁹³

The stimulation of tumor cell proliferation by CXCL12 may be MAPK-dependent.^{97–99} CXCL12 can activate Ras and MAPK.¹⁰⁰ Activated MAPK upregulates various transcription factors, including c-Myc, which can upregulate the expression of CXCR4.¹⁹ In short, CXCL12/CXCR4 can activate the MAPK pathway, resulting in tumor cell proliferation, which in turn activates MAPK, which upregulates CXCR4 via transcription factors. Thus, there may be a positive feedback loop that promotes CXCR4 expression and further amplifies MAPK signaling.¹⁹

Furthermore, CXCL12 can modulate tumor growth via activating the PI3K/Akt pathway.^{97–99} Wnt signaling also has an important role in the CXCL12-induced proliferation of cancer cells. In *in vitro* studies, Wang *et al.*¹⁰¹ observed that CXCR4 modulated the canonical Wnt pathway and that blockade of CXCL12/CXCR4 signaling inhibited pancreatic cancer proliferation and progression *in vitro* via inactivation of the canonical Wnt pathway.

Recent evidence indicates that tumor–stromal cell interactions have a crucial role in tumor initiation and progression.¹⁰³ The tumor microenvironment includes cellular components (fibroblasts, immune cells and endothelial cells), extracellular matrix proteins, proteolytic enzymes, growth factors and inflammatory cytokines; together, these support the tumor’s structure, growth and angiogenesis. Physiologically, CXCL12 is mainly expressed by mesenchymal stromal cells in various organs, such as the liver, lungs and bone marrow (BM). CXCR4-positive cancer cells can be recruited to these CXCL12-rich mesenchymal stroma niches^{101,104,105} to initiate metastasis (Figure 3).

Furthermore, CXCL12 can attract CXCR4-positive immune cells or fibroblasts to the tumor sites to assist tumor development. High CXCL12 levels in tumors attract CXCR4-positive inflammatory, vascular and stromal cells into the tumor mass; together, these cells support tumor growth by secreting growth factors, cytokines, chemokines and pro-angiogenic factors.¹⁰⁶ A recent study reported that CXCL12 secreted by multiple myeloma (MM) cells can attract CXCR4-expressing monocytes to the MM niche. These monocytes undergo differentiation and become macrophages that significantly increase the proliferation of MM cell lines and protect MM cells from chemotherapy- and immunotherapy-induced cell death.¹⁰⁷ In addition, macrophages strongly induce the expression of CCL2, CCL5, IL-1 β and IL-8 in MM cells, establishing a tumor-favorable microenvironment.¹⁰⁷

Increasing evidence suggests that the CXCR4 expression level in cancer cells is positively correlated with microvessel density in many cancer types, including breast cancer, prostate cancer and glioma. Furthermore, researchers have detected CXCR4 expression in tumor-infiltrating plasma cells and the endothelial cells of large vessels in tumor stroma,²⁹ demonstrating that the CXCL12/ CXCR4 interaction has an important role in tumor angiogenesis.

There are four possible mechanisms of the effects of CXCL12/CXCR4 on tumor angiogenesis: (1) CXCL12 upregulates VEGF expression in tumor tissue by activating the PI3K/Akt signaling pathway in cancer cells, promoting vascularization.¹¹¹ VEGF facilitates cancer cells' migration to CXCL12 via inducing CXCR4 expression.¹¹² In ovarian cancer, pathologic concentrations of VEGF and CXCL12 efficiently and synergistically induce *in vivo* angiogenesis.¹¹³ Thus, there may be a regenerative feedback loop between CXCL12/CXCR4 and VEGF that facilitates angiogenesis. (2) CXCL12 reduces glycolytic enzyme phosphoglycerate kinase 1 (PGK1) expression, which leads to the increased secretion of VEGF and thus an angiogenic response in cancer.¹¹⁴ PGK1 is a glycolytic enzyme that catalyses the conversion of 1, 3-diphosphoglycerate to 3-phosphoglycerate. PGK1 can reduce disulfide bonds in the serine protease, which leads to the release of the tumor blood vessel inhibitor, angiostatin. Overexpression of PGK1 can reduce the secretion of VEGF and IL-8 and increases the generation of angiostatin, restraining angiogenesis. CXCL12 can inhibit PGK1 expression and promote angiogenesis. (3) CXCL12 significantly upregulates several angiogenesis-associated genes, such as *interferon- α -inducible protein 27*, *IL-6*, *bone morphogenetic protein-6*, *SOC52* and *cyclooxygenase-2*, in cancer cells. Among them, *IL-6* is the earliest and highest upregulated gene. The transcriptional regulation of IL-6 by CXCL12 was found to be mediated by phosphorylation of ERK1/2 and activation of the NF- κ B complex.¹¹⁵ IL-6 may induce angiogenesis indirectly by inducing the expression of VEGF, fibroblast growth factor, or cyclooxygenase-2.^{116,117} Thus, CXCL12 may enhance angiogenesis via inducing IL-6. (4) CXCL12 can recruit endothelial progenitor cells to the vicinity of neovascularization (Figure 4). Orimo *et al.*¹⁰⁶ showed that the CXCL12 released by carcinoma-associated fibroblasts is responsible for recruiting endothelial progenitor cells into tumor masses, thereby boosting tumor angiogenesis. Meanwhile, another study¹¹⁸ showed that the retention of recruited BM-derived circulating cells in close proximity to angiogenic vessels is mediated by CXCL12. Together, these data suggest that CXCL12 contributes to tumor angiogenesis through multiple signals. Interrupting these pathways will be a novel and efficient anti-angiogenesis strategy to treat cancer.

Cancer infiltration and metastasis is a multistep and complex process. Epithelial-to-mesenchymal transition (EMT) has been recognized as an important process that is associated with cancer metastasis. Recent studies have demonstrated that CXCL12/CXCR4 signaling promotes EMT by activating the MEK/ERK, PI3K/AKT or

Figure 4. CXCL12/CXCR4 promotes angiogenesis in tumors. CXCL12 can induce CXCR4 (+) cancer cells to secrete VEGF and IL-6 to promote angiogenesis in tumors. In addition, CXCL12 can recruit endothelial progenitor cells to sites of neovascularization in tumors to promote angiogenesis.

Wnt/ β -catenin pathway in chondrosarcoma,¹¹⁹ glioblastoma,¹²⁰ colorectal cancer,¹²¹ hepatocellular carcinoma¹²² and pancreatic cancer.¹²³ Thus, therapies that target CXCL12/CXCR4 may be effective by suppressing EMT in cancer.

Muller *et al.*¹²⁴ reported that the liver, BM, lungs and lymph nodes exhibit peak expression levels of CXCL12 and represent the most common organs for homing of breast cancer metastasis, indicating that the organ-specific metastasis of cancer cells is dependent on chemokines (Figure 3). Tumor cells ultimately metastasize to distant organs by the specific binding of chemokines and their receptors. CXCR4/CXCL12 has been implicated in the metastasis of various types of cancer.¹²⁵ For example, Kim *et al.*¹²⁶ verified that CXCR4 is expressed and functional on colorectal cancer cells, and CXCL12 is highly expressed in the liver and may specifically attract colorectal cancer CXCR4 (+) cells. Thus, the liver may be a specific target for CXCR4-expressing colorectal cancer cells because of its relative abundance of CXCL12. *In vivo*, researchers have demonstrated that CXCL12/CXCR4 has a role in metastasis. Gelmini *et al.*¹²⁷ reported that endometrial cancer cells (HEC1A) generated diffuse metastases in the peritoneum, lungs and liver of CD-1 nude mice; however, simultaneous treatment with a neutralizing anti-CXCR4 monoclonal antibody dramatically reduced the number and size of the metastases in these animals. All these findings indicate that after being activated by its ligand CXCL12, CXCR4 initiates the signaling pathway in tumor cells, which can promote metastasis.

At present, the most widely studied and accepted metastasis pathways include the PI3K/Akt, ERK and NF- κ B pathways (Figure 2). In hematologic malignancies¹²⁸ and melanoma,¹²⁹ CXCL12/CXCR4 can stimulate PI3K and modulate the adhesion and migration of cancer cells through diverse downstream signals. Tsukamoto *et al.*¹³⁰ also found that CXCL12/CXCR4 has important roles in the muscular infiltration of endometrial cancer by activating the PI3K/Akt signaling pathway. PI3K/Akt activation might promote the invasion and metastasis of cancer^{95,131,132} by regulating the integrins β_1 (ref. 96) and β_3 ,²¹ VEGF-C⁹⁶ and $\alpha\beta_6$ integrin-mediated uPA expression.¹³³ We conclude that tumor infiltration and metastasis, mediated by CXCL12, is partially PI3K/Akt-dependent.

CXCL12 acts through CXCR4 to activate the MEK/ERK/NF- κ B pathway, contributing to the migration of human osteosarcoma cells. The results of a recent study indicated that CXCL12/CXCR4 promote metastasis in oral squamous cell carcinoma by activating

ERK1/2, Akt/PKB¹³⁴ and NF- κ B.¹³⁵ Activation of the ERK1/2 signaling pathway can increase the activity of matrix metalloproteinase 2 and matrix metalloproteinase 9, increasing the adhesion capability of cancer cells and metastasis.^{136,137}

The basal lamina of endothelial venules is rich in CXCL12,¹³⁸ which may attract CXCR4-positive cancer cells to blood vessels from the primary tumor and thus support hematogenous metastasis. In addition, CXCL12 in peripheral vessels can support and maintain stem cells in stem cell niches. Tumors are often under hypoxic conditions, and CXCL12 expression can be upregulated in endothelial cells by hypoxia-inducible factor-1 α .¹³⁹ Thus, CXCL12 may recruit CXCR4-positive cancer stem cells to the peripheral vessels as a pool for metastasis.¹⁴⁰

These data emphasize the importance of CXCL12/CXCR4 in cancer metastasis and suggest that targeting the molecular components of the signaling pathways described above will provide several important therapeutic opportunities for controlling the progression and metastasis of cancer mediated by CXCL12/CXCR4.

CXCR7 MAY HAVE A DIFFERENT ROLE FROM CXCR4 IN CANCER CELLS

Although CXCL12 can have roles in cancer through binding CXCR4 and CXCR7, CXCR7 may have different roles from CXCR4. First, CXCR7 may be differentially regulated in cancer. For example, E2 enhanced CXCR4 expression but repressed CXCR7 expression in breast cancer cells. A recent study demonstrated that CXCR4 expression was induced by hypoxia-inducible factor-1 α , whereas CXCR7 expression was independent of hypoxia.¹⁴¹ Second, CXCR7 may activate different genes from CXCR4 in cancer. A recent study reported that CXCR4 and CXCR7 are disparate twins in colon cancer. The expression of AXL, C5, IGFBP7, IL-24 and EGFR was increased after exposure to CXCL12 in CXCR4-overexpressing cancer cells, whereas the expression of AKR1C3 and TNNC1 was increased after stimulation with CXCL12 in CXCR7-overexpressing cancer cells. AXL, C5, IGFBP7, IL-24 and EGFR were assigned to the positive regulation of cell migration, and proliferation, whereas AKR1C3 and TNNC1 were assigned to fatty acid, lipid and cellular lipid metabolic processes.¹⁴² Furthermore, CXCR4-overexpressing cells showed increased sensitivity against 5-fluorouracil, whereas CXCR7-overexpressing cells were more chemoresistant, indicating that CXCR7 may have different roles from CXCR4 in cancer cells. Thus, further studies may be required to elucidate the exact role of CXCR7 in cancer.

Several reports have shown that CXCR7 can activate intracellular signaling pathways, including AKT, MAPK and JAK2/STAT3, promoting cancer development and progression¹⁴³ (Figure 2). In addition, CXCL12/CXCR7 enhanced ovarian cancer cell invasion by upregulating matrix metalloproteinase 9 expression through the p38 MAPK pathway.⁴⁰ Thus, targeting CXCR7 may provide a new treatment for cancer.

CXCL12 IN TUMOR IMMUNOSUPPRESSION AND IMMUNOTHERAPY

As a pleiotropic chemokine, CXCL12 participates in the regulation of tissue homeostasis, immune surveillance, autoimmunity and cancer. First, the constitutive expression of CXCL12 in the BM and other tissues is responsible for regulating the trafficking and localization of immature and maturing leukocytes to these tissues, holding tissue homeostasis.¹⁴⁴ Moreover, CXCL12, through CXCR4, has an important role in maintaining neutrophil homeostasis. CXCL12 can direct the migration of neutrophils to organs, particularly immune-privileged organs, as part of immune surveillance of the body.¹⁴⁴

CXCR7 is expressed by lymphocytes and granulocytes in the BM, whereas it is expressed by monocytes, granulocytes and

Table 1. CXCL12/CXCR4 inhibition in cancer

Agent	Additional agent	Effects on tumors
CXCR4 antagonist AMD3100		Reduced metastatic spread and improved overall survival in an orthotopic ovarian cancer model ¹⁴⁷ Suppressed effect of CXCL12 on tumorigenesis ⁹⁵ Reduced growth of ovarian cancer cells and intraperitoneal dissemination and improved survival of mice with ovarian cancer ^{159,161,162} Suppressed biological effects of CXCL12 on ovarian cancer cells ¹⁶⁰
	Cisplatin	Decreased tumor burden in mice more significantly than did either agent as monotherapy ¹⁷⁰
	Vincristine	Extended the survival of mice with ALL ¹⁷¹
	Docetaxel	Exerted increased antitumor effect compared with docetaxel alone ¹⁷²
CTCE-9908		Induced multinucleation, G(2)-M arrest and abnormal mitosis in ovarian cancer cells ¹⁶⁶
	Paclitaxel	Led to additive cytotoxicity ¹⁶⁶
NOX-A12	Irradiation	Led to longer survival of rats with brain tumors induced by n-ethyl-N-nitrosourea ¹⁷⁴
	Bendamustine	Sensitized CLL cells to Bendamustine or Fludarabine in BMSC cocultures ¹⁷³
	Fludarabine	

Abbreviations: ALL, acute lymphoblastic leukemia; BMSC, bone marrow stromal cell; CLL, chronic lymphocytic leukemia.

platelets among peripheral blood cells.¹³ In the immune system, CXCR7 is expressed in B cells and dendritic cells. Studies demonstrated that CXCR7 is required for mature B-cell function and for the survival and differentiation of the switch memory cohort¹⁴⁵ and that it may be important at the beginning of the innate immune response.¹³

Recently, immunotherapy has emerged as a promising treatment strategy. Recent studies showed that CXCL12 contributes to tumor immune suppression by recruiting specific immune cell populations.¹⁴⁶ Thus, blocking CXCL12/CXCR4 may decrease immune suppression in cancer. The delivery of a CXCR4 antagonist-expressing oncolytic vaccinia virus could decrease immune suppression by decreasing the numbers of endothelial cells, myeloid cells, plasmacytoid dendritic cells and T-regulatory cells, leading to the reduced metastatic spread of tumors and improved overall survival in a mouse model.¹⁴⁷ Similar findings were reported in breast cancer mouse model.¹⁴⁸ Thus, the application of CXCR4 antagonist represents a potent therapy for cancer.

In pancreatic ductal adenocarcinoma, depleting carcinoma-associated fibroblasts that express fibroblast activation protein could help to achieve immune control of PDA growth. Fibroblast activation protein (+) carcinoma-associated fibroblasts were the principal source of CXCL12 in pancreatic ductal adenocarcinoma, and cancer cells were coated with CXCL12, leading to the absence of T cells from regions of tumor-containing cancer cells. Administering AMD3100, a CXCR4 inhibitor, induced rapid T-cell accumulation among cancer cells and diminished cancer cells.¹⁴⁹ AMD3100 is a kind of CXCR4 antagonist that was reported to inhibit immune suppression.¹⁵⁰ Studies revealed that blocking CXCL12/CXCR4 with AMD3100 prevents ultraviolet (UV) radiation-induced immune suppression and skin cancer.^{151,152} AMD3100 also prevented polarization toward an immune-suppressive microenvironment, inhibited tumor growth, reduced lung metastasis and improved survival in hepatocellular carcinoma models.¹⁵³ CXCL12 can recruit regulatory T cells to the BM, and regulatory T cells may form an immunosuppressive niche to facilitate cancer bone metastasis and contribute to bone deposition.¹⁵⁴ In B-cell lymphoma, AMD3100 enhances antilymphoma effects by blocking regulatory T recruitment toward the lymphoma tissue.¹⁵⁵

CXCL12/CXCR4 IN ANTICANCER THERAPIES

Blocking the CXCL12 pathway may be a valid strategy for targeting various components in cancer,^{156,157} such as CXCR4 and CXCR7. Thus, it is urgent that we gain a deep understanding

of the CXCL12/CXCR4 pathway in preclinical studies to inform the future translation of CXCL12, CXCR4 or CXCR7 inhibitors into clinical use. So far, several molecules have been developed that target CXCR4 or CXCL12 and thus interfere with tumor growth, including the anti-CXCR4 drugs AMD3100 and AMD3465, the CXCL12 analog peptide CTCE-9908, the anti-CXCL12 aptamer Nox-A12 and the CXCR7-specific inhibitor CCX2066 (Table 1).³⁹

AMD3100, a CXCR4 antagonist, was demonstrated to block CXCL12-induced HER2/neu activation *in vitro* and inhibit tumor growth *in vivo*.¹⁵⁸ The effects of CXCL12 on tumorigenesis were inhibited by AMD3100.^{95,159,160} Treatment with AMD3100 blocked ligand–receptor binding reduced the growth of ovarian cancer cells and intraperitoneal dissemination, and modestly improved the overall survival of mice with metastatic ovarian cancer.^{159,161,162} In adult T-cell leukemia, AMD3100 inhibited both the CXCL12-induced migration and phosphorylation of ERK1/2 and the infiltration of lymphomatous cells into liver and lung tissues *in vivo*.¹⁶³

AMD3465, a monocyclam, is also a CXCR4 antagonist. AMD3465 induces the mobilization of acute myeloid leukemia cells and endothelial progenitor cells into the circulation and enhances the antileukemic activity of chemotherapy, prolonging animal survival.¹⁶⁴ Thus, the combination of AMD3465 and chemotherapy may provide promising therapy for cancer. In addition, the cyclopentapeptide FC131, a new CXCR4 antagonist, can also bind CXCR4 and inhibit CXCL12-mediated activation on the basis of ligand modification, receptor mutagenesis and computational modeling approaches.¹⁶⁵

CTCE-9908, a small analog peptide, consists of a dimer of CXCL12 and acts as a competitive inhibitor of CXCL12, which can suppress CXCL12 secretion. CTCE-9908 was found to deregulate DNA damage checkpoint proteins and spindle assembly checkpoint proteins at the G (2)–M phases of the cell cycle.¹⁶⁶ Furthermore, combined treatment with CTCE-9908 and the drug paclitaxel led to additive cytotoxicity that also involved mitotic catastrophe.¹⁶⁶

Blocking the CXCL12 pathway alone may not be sufficient. Several recent studies have revealed that certain chemotherapeutic agents, vascular-disrupting agents and radiation can activate the CXCL12 pathway.^{167,168} Thus, therapy-induced activation of the CXCL12 pathway may have a role in resistance to cytotoxic therapy.¹⁶⁹ The use of anti-CXCL12 therapy in combination with other anticancer therapies has shown promising efficacy in many studies. For example, combination therapy with AMD3100 and cisplatin significantly decreased the tumor burden in mice compared with either agent as monotherapy.¹⁷⁰ In human ALL, AMD3100 increased the efficacy of the cell cycle-specific drug

vincristine, resulting in extended survival of non-obese diabetes severe combined immunodeficient (NOD/SCID) mice with ALL.¹⁷¹ In another study, the combination of docetaxel and AMD3100 exerted a greater antitumor effect than did docetaxel alone.¹⁷² Therefore, clinical trials should be feasible with the development of novel orally available CXCR4 inhibitors combined with chemotherapy.

Moreover, CXCR4 blockade with AMD3100 may not be sufficient to block the effects of CXCL12, which can also bind to CXCR7 on cancer and stromal cells. This effect can be studied using Nox-A12, an aptamer against CXCL12, or CXCR7-specific inhibitors, such as CCX2066.³⁹ Nox-A12 is an l-enantiomeric RNA oligonucleotide that binds and inhibits CXCL12 with high affinity. In recent studies, NOX-A12 inhibited CXCL12-induced chemotaxis of CLL cells and sensitized CLL cells to bendamustine and fludarabine.¹⁷³ Furthermore, treatment with NOX-A12 prolonged the lifespans of irradiated rats with glioblastoma.¹⁷⁴ Another study reported that NOX-A12 mobilized white blood cells and hematopoietic stem and progenitor cells into the peripheral blood. In healthy volunteers, single doses of NOX-A12 dose-dependently mobilized white blood cells and hematopoietic stem cells into the peripheral blood,¹⁷⁵ indicating that NOX-A12 is appropriate for therapeutic use in hematological cancer cells.

Recently, researchers have found new drugs that target CXCL12, such as the high-affinity antistromal-derived factor-1 PEGylated mirror-image l-oligonucleotide (olaptesed-pegol). Using this drug in BM niches rendered the microenvironment less receptive to MM cells and reduced MM cell homing and growth, thereby inhibiting MM metastasis in the BM.¹⁷⁶

CONCLUDING REMARKS

In conclusion, an abundance of studies have shown that CXCL12 has a vital role in tumor development. CXCL12 can activate various signaling pathways of cancer cells in an autocrine or paracrine manner, provoke cancer cell multiplication and infiltration, suppress apoptosis and promote angiogenesis in cancer tissue. The ligand can also attract stromal cells and stimulate them to secrete growth factors to support tumor growth and angiogenesis. Consequently, inhibition of the CXCL12/CXCR4 axis may be a new approach to targeted therapy for cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *Ca Cancer J Clin* 2014; **64**: 9–29.
- Barbieri F, Bajetto A, Florio T. Role of chemokine network in the development and progression of ovarian cancer: a potential novel pharmacological target. *J Oncol* 2010; **2010**: 426956.
- Ganzfried BF, Riester M, Haibe-Kains B, Risch T, Tyekucheva S, Jazic I et al. curatedOvarianData: clinically annotated data for the ovarian cancer transcriptome. *Database* 2013; **2013**: bat013.
- Madden SF, Clarke C, Stordal B, Carey MS, Broadus R, Gallagher WM et al. OvMark: a user-friendly system for the identification of prognostic biomarkers in publicly available ovarian cancer gene expression datasets. *Mol Cancer* 2014; **13**: 241.
- Shirozu M, Nakano T, Inazawa J, Tashiro K, Tada H, Shinohara T et al. Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene. *Genomics* 1995; **28**: 495–500.
- Yu Y, Xiao CH, Tan LD, Wang QS, Li XQ, Feng YM. Cancer-associated fibroblasts induce epithelial-mesenchymal transition of breast cancer cells through paracrine TGF-beta signalling. *Br J Cancer* 2014; **110**: 724–732.
- Guyon A. CXCL12 chemokine and its receptors as major players in the interactions between immune and nervous systems. *Front Cell Neurosci* 2014; **8**: 65.
- Lee YH, Noh TW, Lee MK, Jameson JL, Lee EJ. Absence of activating mutations of CXCR4 in pituitary tumours. *Clin Endocrinol* 2010; **72**: 209–213.
- Crowther-Swanepoel D, Qureshi M, Dyer MJ, Matutes E, Dearden C, Catovsky D et al. Genetic variation in CXCR4 and risk of chronic lymphocytic leukemia. *Blood* 2009; **114**: 4843–4846.
- Ierano C, Giuliano P, D'Alterio C, Cioffi M, Mettievier V, Portella L et al. A point mutation (G574A) in the chemokine receptor CXCR4 detected in human cancer cells enhances migration. *Cell Cycle* 2009; **8**: 1228–1237.
- Archibald KM, Kulbe H, Kwong J, Chakravarty P, Temple J, Chaplin T et al. Sequential genetic change at the TP53 and chemokine receptor CXCR4 locus during transformation of human ovarian surface epithelium. *Oncogene* 2012; **31**: 4987–4995.
- Ghanem I, Riveiro ME, Paradis V, Faivre S, de Parga PM, Raymond E. Insights on the CXCL12-CXCR4 axis in hepatocellular carcinoma carcinogenesis. *Am J Transl Res* 2014; **6**: 340–352.
- Sanchez-Martin L, Sanchez-Mateos P, Cabanas C. CXCR7 impact on CXCL12 biology and disease. *Trend Mol Med* 2013; **19**: 12–22.
- Liu Y, Carson-Walter E, Walter KA. Chemokine receptor CXCR7 is a functional receptor for CXCL12 in brain endothelial cells. *PLoS ONE* 2014; **9**: e103938.
- 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.
- Liu F, Lang R, Wei J, Fan Y, Cui L, Gu F et al. Increased expression of SDF-1/CXCR4 is associated with lymph node metastasis of invasive micropapillary carcinoma of the breast. *Histopathology* 2009; **54**: 741–750.
- Iwasa S, Yanagawa T, Fan J, Katoh R. Expression of CXCR4 and its ligand SDF-1 in intestinal-type gastric cancer is associated with lymph node and liver metastasis. *Anticancer Res* 2009; **29**: 4751–4758.
- Liang JJ, Zhu S, Bruggeman R, Zaino RJ, Evans DB, Fleming JB et al. High levels of expression of human stromal cell-derived factor-1 are associated with worse prognosis in patients with stage II pancreatic ductal adenocarcinoma. *Cancer Epidemiol, Biomarker Prev* 2010; **19**: 2598–2604.
- Thomas RM, Kim J, Revelo-Penafiel MP, Angel R, Dawson DW, Lowy AM. The chemokine receptor CXCR4 is expressed in pancreatic intraepithelial neoplasia. *Gut* 2008; **57**: 1555–1560.
- Guo L, Cui ZM, Zhang J, Huang Y. Chemokine axes CXCL12/CXCR4 and CXCL16/CXCR6 correlate with lymph node metastasis in epithelial ovarian carcinoma. *Chin J Cancer* 2011; **30**: 336–343.
- Yu Y, Shi X, Shu Z, Xie T, Huang K, Wei L et al. Stromal cell-derived factor-1 (SDF-1)/CXCR4 axis enhances cellular invasion in ovarian carcinoma cells via integrin beta1 and beta3 expressions. *Oncol Res* 2014; **21**: 217–225.
- Huang Y, Zhang J, Cui ZM, Zhao J, Zheng Y. Expression of the CXCL12/CXCR4 and CXCL16/CXCR6 axes in cervical intraepithelial neoplasia and cervical cancer. *Chin J Cancer* 2013; **32**: 289–296.
- Meng X, Wuyi L, Yuhong X, Xinming C. Expression of CXCR4 in oral squamous cell carcinoma: correlations with clinicopathology and pivotal role of proliferation. *J Oral Pathol Med* 2010; **39**: 63–68.
- Agarwal A, Cooke L, Riley C, Qi W, Mount D, Mahadevan D. Genetic and cytokine changes associated with symptomatic stages of CLL. *Leuk Res* 2014; **38**: 1097–1101.
- Barbolina MV, Kim M, Liu Y, Shepard J, Belmadani A, Miller RJ et al. Microenvironmental regulation of chemokine (C-X-C-motif) receptor 4 in ovarian carcinoma. *Mol Cancer Res* 2010; **8**: 653–664.
- Popple A, Durrant LG, Spendlove I, Roland P, Scott IV, Deen S et al. The chemokine, CXCL12, is an independent predictor of poor survival in ovarian cancer. *Br J Cancer* 2012; **106**: 1306–1313.
- Bignotti E, Tassi RA, Calza S, Ravaggi A, Bandiera E, Rossi E et al. Gene expression profile of ovarian serous papillary carcinomas: identification of metastasis-associated genes. *Am J Obstet Gynecol* 2007; **19**: e241–211.
- Wertel I, Polak G, Tarkowski R, Kotarska M. SDF-1alpha/CXCL12 and dendritic cells in ovarian cancer microenvironment. *Ginekol Pol* 2011; **82**: 421–425.
- Jiang YP, Wu XH, Shi B, Wu WX, Yin GR. Expression of chemokine CXCL12 and its receptor CXCR4 in human epithelial ovarian cancer: an independent prognostic factor for tumor progression. *Gynecol Oncol* 2006; **103**: 226–233.

- 30 Sanz-Pamplona R, Garcia-Garcia J, Franco S, Messegueur X, Driouch K, Oliva B *et al*. A taxonomy of organ-specific breast cancer metastases based on a protein-protein interaction network. *Mol Biosyst* 2012; **8**: 2085–2096.
- 31 Lim JB, Chung HW. Serum ENA78/CXCL5, SDF-1/CXCL12, and their combinations as potential biomarkers for prediction of the presence and distant metastasis of primary gastric cancer. *Cytokine* 2015; **73**: 16–22.
- 32 de Lourdes Perim A, Guembarovski RL, Oda JM, Lopes LF, Ariza CB, Amarante MK *et al*. CXCL12 and TP53 genetic polymorphisms as markers of susceptibility in a Brazilian children population with acute lymphoblastic leukemia (ALL). *Mol Biol Rep* 2013; **40**: 4591–4596.
- 33 Monteagudo C, Ramos D, Pellin-Carcelen A, Gil R, Callaghan RC, Martin JM *et al*. CCL27-CCR10 and CXCL12-CXCR4 chemokine ligand-receptor mRNA expression ratio: new predictive factors of tumor progression in cutaneous malignant melanoma. *Clin Exp Metastasis* 2012; **29**: 625–637.
- 34 Quattrocchi L, Sisson M, Green A, Martin SG, Durrant L, Deen S. Expression of angiogenic chemokines in ovarian clear cell carcinoma. *J Obstet Gynaecol Res* 2013; **39**: 297–304.
- 35 Jaszczynska-Nowinka K, Rucinski M, Ziolkowska A, Markowska A, Malendowicz LK. Expression of and transcript variants and in epithelial ovarian cancer. *Oncol Lett* 2014; **7**: 1618–1624.
- 36 Chatterjee S, Behnam Azad B, Nimmagadda S. The intricate role of CXCR4 in cancer. *Adv Cancer Res* 2014; **124**: 31–82.
- 37 Su YC, Wu MT, Huang CJ, Hou MF, Yang SF, Chai CY. Expression of CXCR4 is associated with axillary lymph node status in patients with early breast cancer. *Breast* 2006; **15**: 533–539.
- 38 Wagner PL, Hyjek E, Vazquez MF, Meherally D, Liu YF, Chadwick PA *et al*. CXCL12 and CXCR4 in adenocarcinoma of the lung: association with metastasis and survival. *J Thorac Cardiovasc Surg* 2009; **137**: 615–621.
- 39 Duda DG, Kozin SV, Kirkpatrick ND, Xu L, Fukumura D, Jain RK. CXCL12 (SDF1alpha)-CXCR4/CXCR7 pathway inhibition: an emerging sensitizer for anticancer therapies? *Clin Cancer Res* 2011; **17**: 2074–2080.
- 40 Yu Y, Li H, Xue B, Jiang X, Huang K, Ge J *et al*. SDF-1/CXCR7 axis enhances ovarian cancer cell invasion by MMP-9 expression through p38 MAPK pathway. *DNA Cell Biol* 2014; **33**: 543–549.
- 41 Zhou W, Jiang Z, Liu N, Xu F, Wen P, Liu Y *et al*. Down-regulation of CXCL12 mRNA expression by promoter hypermethylation and its association with metastatic progression in human breast carcinomas. *J Cancer Res Clin Oncol* 2009; **135**: 91–102.
- 42 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. *Digest Dis Sci* 2012; **57**: 650–659.
- 43 Ramos EA, Camargo AA, Braun K, Slowik R, Cavalli IJ, Ribeiro EM *et al*. Simultaneous CXCL12 and ESR1 CpG island hypermethylation correlates with poor prognosis in sporadic breast cancer. *BMC Cancer* 2010; **10**: 23.
- 44 Ramos EA, Grochowski M, Braun-Prado K, Seniski GG, Cavalli IJ, Ribeiro EM *et al*. Epigenetic changes of CXCR4 and its ligand CXCL12 as prognostic factors for sporadic breast cancer. *PLoS ONE* 2011; **6**: e29461.
- 45 Pietkiewicz PP, Lutkowska A, Lianeri M, Jagodzinski PP. Tamoxifen epigenetically modulates CXCL12 expression in MCF-7 breast cancer cells. *Biomed Pharmacother* 2010; **64**: 54–57.
- 46 Kajiyama H, Shibata K, Ino K, Nawa A, Mizutani S, Kikkawa F. Possible involvement of SDF-1alpha/CXCR4-DPP4 axis in TGF-beta1-induced enhancement of migratory potential in human peritoneal mesothelial cells. *Cell Tissue Res* 2007; **330**: 221–229.
- 47 Kulbe H, Thompson R, Wilson JL, Robinson S, Hagemann T, Fatah R *et al*. The inflammatory cytokine tumor necrosis factor-alpha generates an autocrine tumor-promoting network in epithelial ovarian cancer cells. *Cancer Res* 2007; **67**: 585–592.
- 48 Kulbe H, Hagemann T, Szlosarek PW, Balkwill FR, Wilson JL. The inflammatory cytokine tumor necrosis factor-alpha regulates chemokine receptor expression on ovarian cancer cells. *Cancer Res* 2005; **65**: 10355–10362.
- 49 Boudot A, Kerdivel G, Habauzit D, Eeckhoutte J, Le Dily F, Flouriot G *et al*. Differential estrogen-regulation of CXCL12 chemokine receptors, CXCR4 and CXCR7, contributes to the growth effect of estrogens in breast cancer cells. *PLoS ONE* 2011; **6**: e20898.
- 50 Hall JM, Korach KS. Stromal cell-derived factor 1, a novel target of estrogen receptor action, mediates the mitogenic effects of estradiol in ovarian and breast cancer cells. *Mol Endocrinol* 2003; **17**: 792–803.
- 51 Chen L, Xu S, Zeng X, Li J, Yin W, Chen Y *et al*. c-myc activates CXCL12 transcription in T47D and MCF7 breast cancer cells. *Acta Biochim Biophys Sin* 2010; **42**: 1–7.
- 52 Uygun B, Wu WS. SLUG promotes prostate cancer cell migration and invasion via CXCR4/CXCL12 axis. *Mol Cancer* 2011; **10**: 139.
- 53 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.
- 54 Martin SK, Diamond P, Williams SA, To LB, Peet DJ, Fujii N *et al*. Hypoxia-inducible factor-2 is a novel regulator of aberrant CXCL12 expression in multiple myeloma plasma cells. *Haematologica* 2010; **95**: 776–784.
- 55 Lin SY, Dolfi SC, Amiri S, Li J, Budak-Alpdogan T, Lee KC *et al*. P53 regulates the migration of mesenchymal stromal cells in response to the tumor micro-environment through both CXCL12-dependent and -independent mechanisms. *Int J Oncol* 2013; **43**: 1817–1823.
- 56 Kojima K, McQueen T, Chen Y, Jacamo R, Konopleva M, Shinjima N *et al*. p53 activation of mesenchymal stromal cells partially abrogates microenvironment-mediated resistance to FLT3 inhibition in AML through HIF-1alpha-mediated down-regulation of CXCL12. *Blood* 2011; **118**: 4431–4439.
- 57 Moskovits N, Kalinkovich A, Bar J, Lapidot T, Oren M. p53 attenuates cancer cell migration and invasion through repression of SDF-1/CXCL12 expression in stromal fibroblasts. *Cancer Res* 2006; **66**: 10671–10676.
- 58 Douglass S, Meeson AP, Overbeck-Zubrzycka D, Brain JG, Bennett MR, Lamb CA *et al*. Breast cancer metastasis: demonstration that FOXp3 regulates CXCR4 expression and the response to CXCL12. *J Pathol* 2014; **234**: 74–85.
- 59 Jeon ES, Moon HJ, Lee MJ, Song HY, Kim YM, Cho M *et al*. Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblast-like cells. *Stem Cells* 2008; **26**: 789–797.
- 60 Wang H, Liu W, Wei D, Hu K, Wu X, Yao Y. Effect of the LPA-mediated CXCL12-CXCR4 axis in the tumor proliferation, migration and invasion of ovarian cancer cell lines. *Oncol Lett* 2014; **7**: 1581–1585.
- 61 Zannettino AC, Buhning HJ, Niutta S, Watt SM, Benton MA, Simmons PJ. The sialomucin CD164 (MGC-24v) is an adhesive glycoprotein expressed by human hematopoietic progenitors and bone marrow stromal cells that serves as a potent negative regulator of hematopoiesis. *Blood* 1998; **92**: 2613–2628.
- 62 Forde S, Tye BJ, Newey SE, Roubelakis M, Smythe J, McGuckin CP *et al*. Endolyn (CD164) modulates the CXCL12-mediated migration of umbilical cord blood CD133+ cells. *Blood* 2007; **109**: 1825–1833.
- 63 Tang J, Zhang L, She X, Zhou G, Yu F, Xiang J *et al*. Inhibiting CD164 expression in colon cancer cell line HCT116 leads to reduced cancer cell proliferation, mobility, and metastasis *in vitro* and *in vivo*. *Cancer Invest* 2012; **30**: 380–389.
- 64 Huang AF, Chen MW, Huang SM, Kao CL, Lai HC, Chan JY. CD164 regulates the tumorigenesis of ovarian surface epithelial cells through the SDF-1alpha/CXCR4 axis. *Mol Cancer* 2013; **12**: 115.
- 65 Ko SY, Barengo N, Ladanyi A, Lee JS, Marini F, Lengyel E *et al*. HOXA9 promotes ovarian cancer growth by stimulating cancer-associated fibroblasts. *J Clin Invest* 2012; **122**: 3603–3617.
- 66 Qu QX, Huang Q, Xu J, Duan LT, Zhu YB, Zhang XG. CD40 signal regulates CXCR4 mediating ovarian carcinoma cell migration: implications for extrapelvic metastatic factors. *Oncol Res* 2013; **20**: 383–392.
- 67 Kang KS, Choi YP, Gao MQ, Kang S, Kim BG, Lee JH *et al*. CD24(+) ovary cancer cells exhibit an invasive mesenchymal phenotype. *Biochem Biophys Res Commun* 2013; **432**: 333–338.
- 68 Obermajer N, Muthuswamy R, Odunsi K, Edwards RP, Kalinski P. PGE(2)-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment. *Cancer Res* 2011; **71**: 7463–7470.
- 69 Wei S, Kryczek I, Edwards RP, Zou L, Szeliga W, Banerjee M *et al*. Interleukin-2 administration alters the CD4+FOXP3+ T-cell pool and tumor trafficking in patients with ovarian carcinoma. *Cancer Res* 2007; **67**: 7487–7494.
- 70 Leone V, D'Angelo D, Rubio I, de Freitas PM, Federico A, Colamaio M *et al*. MiR-1 is a tumor suppressor in thyroid carcinogenesis targeting CCND2, CXCR4, and SDF-1alpha. *J Clin Endocrinol Metab* 2011; **96**: E1388–E1398.
- 71 Taverna S, Amodeo V, Saieva L, Russo A, Giallombardo M, De Leo G *et al*. Exosomal shuttling of miR-126 in endothelial cells modulates adhesive and migratory abilities of chronic myelogenous leukemia cells. *Mol Cancer* 2014; **13**: 169.
- 72 Zhang Y, Yang P, Sun T, Li D, Xu X, Rui Y *et al*. miR-126 and miR-126* repress recruitment of mesenchymal stem cells and inflammatory monocytes to inhibit breast cancer metastasis. *Nat Cell Biol* 2013; **15**: 284–294.
- 73 Buechli ME, Lamarre J, Koch TG. MicroRNA-140 expression during chondrogenic differentiation of equine cord blood-derived mesenchymal stromal cells. *Stem Cells Dev* 2013; **22**: 1288–1296.
- 74 Huang Z, Shi T, Zhou Q, Shi S, Zhao R, Shi H *et al*. miR-141 regulates colonic leukocytic trafficking by targeting CXCL12beta during murine colitis and human Crohn's disease. *Gut* 2014; **63**: 1247–1257.
- 75 Hsieh JY, Huang TS, Cheng SM, Lin WS, Tsai TN, Lee OK *et al*. miR-146a-5p circuitry uncouples cell proliferation and migration, but not differentiation, in human mesenchymal stem cells. *Nucleic Acids Res* 2013; **41**: 9753–9763.
- 76 Lu MH, Hu CJ, Chen L, Peng X, Chen J, Hu JY *et al*. miR-27b represses migration of mouse MSCs to burned margins and prolongs wound repair through silencing SDF-1a. *PLoS ONE* 2013; **8**: e68972.

- 77 Staton AA, Knaut H, Giraldez AJ. miRNA regulation of Sdf1 chemokine signaling provides genetic robustness to germ cell migration. *Nat Genet* 2011; **43**: 204–211.
- 78 Pillai MM, Yang X, Balakrishnan I, Bemis L, Torok-Storb B. MiR-886-3p down regulates CXCL12 (SDF1) expression in human marrow stromal cells. *PLoS ONE* 2010; **5**: e14304.
- 79 Lu J, Luo H, Liu X, Peng Y, Zhang B, Wang L et al. miR-9 targets CXCR4 and functions as a potential tumor suppressor in nasopharyngeal carcinoma. *Carcinogenesis* 2014; **35**: 554–563.
- 80 Yu T, Liu K, Wu Y, Fan J, Chen J, Li C et al. MicroRNA-9 inhibits the proliferation of oral squamous cell carcinoma cells by suppressing expression of CXCR4 via the Wnt/beta-catenin signaling pathway. *Oncogene* 2014; **33**: 5017–5027.
- 81 Liu Y, Zhou Y, Feng X, An P, Quan X, Wang H et al. MicroRNA-126 functions as a tumor suppressor in colorectal cancer cells by targeting CXCR4 via the AKT and ERK1/2 signaling pathways. *Int J Oncol* 2014; **44**: 203–210.
- 82 Spinello I, Quaranta MT, Riccioni R, Riti V, Pasquini L, Boe A et al. MicroRNA-146a and AMD3100, two ways to control CXCR4 expression in acute myeloid leukemias. *Blood Cancer J* 2011; **1**: e26.
- 83 Liu Z, Ye P, Wang S, Wu J, Zhang A et al. MicroRNA-150 protects the heart from injury by inhibiting monocyte accumulation in a mouse model of acute myocardial infarction. *Circ Cardiovasc Genet* 2014; **8**: 11–20.
- 84 Zhou J, Liu R, Wang Y, Tang J, Tang S, Chen X et al. miR-199a-5p regulates the expression of metastasis-associated genes in B16F10 melanoma cells. *Int J Clin Exp Pathol* 2014; **7**: 7182–7190.
- 85 Shen PF, Chen XQ, Liao YC, Chen N, Zhou Q, Wei Q et al. MicroRNA-494-3p targets CXCR4 to suppress the proliferation, invasion, and migration of prostate cancer. *Prostate* 2014; **74**: 756–767.
- 86 Duan FT, Qian F, Fang K, Lin KY, Wang WT, Chen YQ. miR-133b, a muscle-specific microRNA, is a novel prognostic marker that participates in the progression of human colorectal cancer via regulation of CXCR4 expression. *Mol Cancer* 2013; **12**: 164.
- 87 Luo HN, Wang ZH, Sheng Y, Zhang Q, Yan J, Hou J et al. MiR-139 targets CXCR4 and inhibits the proliferation and metastasis of laryngeal squamous carcinoma cells. *Med Oncol* 2014; **31**: 789.
- 88 Zhu S, Sachdeva M, Wu F, Lu Z, Mo YY. Ubc9 promotes breast cell invasion and metastasis in a sumoylation-independent manner. *Oncogene* 2010; **29**: 1763–1772.
- 89 Toritsuka M, Kimoto S, Muraki K, Landek-Salgado MA, Yoshida A, Yamamoto N et al. Deficits in microRNA-mediated Cxcr4/Cxcl12 signaling in neurodevelopmental deficits in a 22q11 deletion syndrome mouse model. *Proc Natl Acad Sci USA* 2013; **110**: 17552–17557.
- 90 de Nigris F, Schiano C, Infante T, Napoli C. CXCR4 inhibitors: tumor vasculature and therapeutic challenges. *Recent Pat Anticancer Drug Discov* 2012; **7**: 251–264.
- 91 Yang-Hartwich Y, Gurra-Soteras M, Sumi N, Joo WD, Holmberg JC, Craveiro V et al. Ovulation and extra-ovarian origin of ovarian cancer. *Sci Rep* 2014; **4**: 6116.
- 92 Machelon V, Gaudin F, Camilleri-Broet S, Nasreddine S, Bouchet-Delbos L, Pujade-Lauraine E et al. CXCL12 expression by healthy and malignant ovarian epithelial cells. *BMC Cancer* 2011; **11**: 97.
- 93 Porcile C, Bajetto A, Barbieri F, Barbero S, Bonavia R, Biglieri M et al. Stromal cell-derived factor-1alpha (SDF-1alpha/CXCL12) stimulates ovarian cancer cell growth through the EGF receptor transactivation. *Exp Cell Res* 2005; **308**: 241–253.
- 94 Porcile C, Bajetto A, Barbero S, Pirani P, Schettini G. CXCR4 activation induces epidermal growth factor receptor transactivation in an ovarian cancer cell line. *Ann N Y Acad Sci* 2004; **1030**: 162–169.
- 95 Guo Q, Wu XH, Lu YP, Yang B, Xu F, Zhang SJ. [Relationship between chemokine axis CXCL12–CXCR4 and epithelial ovarian cancer]. *Zhonghua Yi Xue Za Zhi* 2013; **93**: 1677–1680.
- 96 Jiang YP, Wu XH, Xing HY, Du XY. [Effect of chemokine CXCL12 and its receptor CXCR4 on proliferation, migration and invasion of epithelial ovarian cancer cells]. *Zhonghua Fu Chan Ke Za Zhi* 2007; **42**: 403–407.
- 97 Darash-Yahana M, Pikarsky E, Abramovitch R, Zeira E, Pal B, Karplus R et al. Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. *FASEB J* 2004; **18**: 1240–1242.
- 98 Barbero S, Bonavia R, Bajetto A, Porcile C, Pirani P, Ravetti JL et al. Stromal cell-derived factor 1alpha stimulates human glioblastoma cell growth through the activation of both extracellular signal-regulated kinases 1/2 and Akt. *Cancer Res* 2003; **63**: 1969–1974.
- 99 Wu M, Chen Q, Li D, Li X, Huang C, Tang Y et al. LRRC4 inhibits human glioblastoma cells proliferation, invasion, and proMMP-2 activation by reducing SDF-1 alpha/CXCR4-mediated ERK1/2 and Akt signaling pathways. *J Cell Biochem* 2008; **103**: 245–255.
- 100 Heinrich EL, Lee W, Lu J, Lowy AM, Kim J. Chemokine CXCL12 activates dual CXCR4 and CXCR7-mediated signaling pathways in pancreatic cancer cells. *J Transl Med* 2012; **10**: 68.
- 101 Wang Z, Ma Q, Liu Q, Yu H, Zhao L, Shen S et al. Blockade of SDF-1/CXCR4 signalling inhibits pancreatic cancer progression *in vitro* via inactivation of canonical Wnt pathway. *Br J Cancer* 2008; **99**: 1695–1703.
- 102 Ganju RK, Brubaker SA, Meyer J, Dutt P, Yang Y, Qin S et al. The alpha-chemokine, stromal cell-derived factor-1alpha, binds to the transmembrane G-protein-coupled CXCR-4 receptor and activates multiple signal transduction pathways. *J Biol Chem* 1998; **273**: 23169–23175.
- 103 Polyak K, Haviv I, Campbell IG. Co-evolution of tumor cells and their micro-environment. *Trends Genet* 2009; **25**: 30–38.
- 104 Bartolome RA, Ferreira S, Miquilena-Colina ME, Martinez-Prats L, Soto-Montenegro ML, Garcia-Bernal D et al. The chemokine receptor CXCR4 and the metalloproteinase MT1-MMP are mutually required during melanoma metastasis to lungs. *Am Pathol* 2009; **174**: 602–612.
- 105 Konopleva MY, Jordan CT. Leukemia stem cells and microenvironment: biology and therapeutic targeting. *J Clin Oncol* 2011; **29**: 591–599.
- 106 Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell* 2005; **121**: 335–348.
- 107 Beider K, Gittner H, Leib M, Gutwein O, Koren-Michowitz M, Ostrovsky O et al. Multiple myeloma cells recruit tumor-supportive macrophages through the CXCR4/CXCL12 axis and promote their polarization toward the M2 phenotype. *Oncotarget* 2014; **5**: 11283–11296.
- 108 Rigo A, Gottardi M, Zamo A, Mauri P, Bonifacio M, Krampera M et al. Macrophages may promote cancer growth via a GM-CSF/HB-EGF paracrine loop that is enhanced by CXCL12. *Mol Cancer* 2010; **9**: 273.
- 109 Ping YF, Yao XH, Jiang JY, Zhao LT, Yu SC, Jiang T et al. The chemokine CXCL12 and its receptor CXCR4 promote glioma stem cell-mediated VEGF production and tumour angiogenesis via PI3K/AKT signalling. *J Pathol* 2011; **224**: 344–354.
- 110 Nervi B, Ramirez P, Rettig MP, Uy GL, Holt MS, Ritchey JK et al. Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100. *Blood* 2009; **113**: 6206–6214.
- 111 Liang Z, Brooks J, Willard M, Liang K, Yoon Y, Kang S et al. CXCR4/CXCL12 axis promotes VEGF-mediated tumor angiogenesis through Akt signaling pathway. *Biochem Biophys Res Commun* 2007; **359**: 716–722.
- 112 Wang J, Sun Y, Song W, Nor JE, Wang CY, Taichman RS. Diverse signaling pathways through the SDF-1/CXCR4 chemokine axis in prostate cancer cell lines leads to altered patterns of cytokine secretion and angiogenesis. *Cell Signal* 2005; **17**: 1578–1592.
- 113 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**: 465–472.
- 114 Wang J, Dai J, Jung Y, Wei CL, Wang Y, Havens AM et al. A glycolytic mechanism regulating an angiogenic switch in prostate cancer. *Cancer Res* 2007; **67**: 149–159.
- 115 Chu CY, Cha ST, Lin WC, Lu PH, Tan CT, Chang CC et al. Stromal cell-derived factor-1alpha (SDF-1alpha/CXCL12)-enhanced angiogenesis of human basal cell carcinoma cells involves ERK1/2-NF-kappaB/interleukin-6 pathway. *Carcinogenesis* 2009; **30**: 205–213.
- 116 Jee SH, Chu CY, Chiu HC, Huang YL, Tsai WL, Liao YH et al. Interleukin-6 induced basic fibroblast growth factor-dependent angiogenesis in basal cell carcinoma cell line via JAK/STAT3 and PI3-kinase/Akt pathways. *J Invest Dermatol* 2004; **123**: 1169–1175.
- 117 Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. *J Biol Chem* 1996; **271**: 736–741.
- 118 Grunewald M, Avraham I, Dor Y, Bachar-Lustig E, Itin A, Jung S et al. VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. *Cell* 2006; **124**: 175–189.
- 119 Yang P, Wang G, Huo H, Li Q, Zhao Y, Liu Y. SDF-1/CXCR4 signaling up-regulates survivin to regulate human sacral chondrosarcoma cell cycle and epithelial-mesenchymal transition via ERK and PI3K/AKT pathway. *Med Oncol* 2015; **32**: 377.
- 120 Liao A, Shi R, Jiang Y, Tian S, Li P, Song F et al. SDF-1/CXCR4 axis regulates cell cycle progression and epithelial-mesenchymal transition via up-regulation of Survivin in glioblastoma. *Mol Neurobiol* 2014; e-pub ahead of print 25 November 2014; doi:10.1007/s12035-014-9006-0.
- 121 Hu TH, Yao Y, Yu S, Han LL, Wang WJ, Guo H et al. SDF-1/CXCR4 promotes epithelial-mesenchymal transition and progression of colorectal cancer by activation of the Wnt/beta-catenin signaling pathway. *Cancer Lett* 2014; **354**: 417–426.
- 122 Li X, Li P, Chang Y, Xu Q, Wu Z, Ma Q et al. The SDF-1/CXCR4 axis induces epithelial-mesenchymal transition in hepatocellular carcinoma. *Mol Cell Biochem* 2014; **392**: 77–84.
- 123 Li X, Ma Q, Xu Q, Liu H, Lei J, Duan W et al. SDF-1/CXCR4 signaling induces pancreatic cancer cell invasion and epithelial-mesenchymal transition *in vitro*

- through non-canonical activation of Hedgehog pathway. *Cancer Lett* 2012; **322**: 169–176.
- 124 Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME et al. Involvement of chemokine receptors in breast cancer metastasis. *Nature* 2001; **410**: 50–56.
- 125 Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer* 2004; **4**: 540–550.
- 126 Kim J, Mori T, Chen SL, Amersi FF, Martinez SR, Kuo C et al. Chemokine receptor CXCR4 expression in patients with melanoma and colorectal cancer liver metastases and the association with disease outcome. *Ann Surg* 2006; **244**: 113–120.
- 127 Gelmini S, Mangoni M, Castiglione F, Beltrami C, Pieralli A, Andersson KL et al. The CXCR4/CXCL12 axis in endometrial cancer. *Clin Exp Metastasis* 2009; **26**: 261–268.
- 128 Niedermeier M, Hennessy BT, Knight ZA, Henneberg M, Hu J, Kurtova AV et al. Isoform-selective phosphoinositide 3'-kinase inhibitors inhibit CXCR4 signaling and overcome stromal cell-mediated drug resistance in chronic lymphocytic leukemia: a novel therapeutic approach. *Blood* 2009; **113**: 5549–5557.
- 129 Monterrubio M, Mellado M, Carrera AC, Rodriguez-Frade JM. PI3Kgamma activation by CXCL12 regulates tumor cell adhesion and invasion. *Biochem Biophys Res Commun* 2009; **388**: 199–204.
- 130 Tsukamoto H, Shibata K, Kajiyama H, Terauchi M, Nawa A, Kikkawa F. Uterine smooth muscle cells increase invasive ability of endometrial carcinoma cells through tumor-stromal interaction. *Clin Exp Metastasis* 2007; **24**: 423–429.
- 131 Ramakrishnan M, Mathur SR, Mukhopadhyay A. Fusion-derived epithelial cancer cells express hematopoietic markers and contribute to stem cell and migratory phenotype in ovarian carcinoma. *Cancer Res* 2013; **73**: 5360–5370.
- 132 Scotton CJ, Wilson JL, Milliken D, Stamp G, Balkwill FR. Epithelial cancer cell migration: a role for chemokine receptors? *Cancer Res* 2001; **61**: 4961–4965.
- 133 Xue B, Wu W, Huang K, Xie T, Xu X, Zhang H et al. Stromal cell-derived factor-1 (SDF-1) enhances cells invasion by alphavbeta6 integrin-mediated signaling in ovarian cancer. *Mol Cell Biochem* 2013; **380**: 177–184.
- 134 Uchida D, Begum NM, Almofti A, Nakashiro K, Kawamata H, Tateishi Y et al. Possible role of stromal-cell-derived factor-1/CXCR4 signaling on lymph node metastasis of oral squamous cell carcinoma. *Exp Cell Res* 2003; **290**: 289–302.
- 135 Rehman AO, Wang CY. CXCL12/SDF-1 alpha activates NF-kappaB and promotes oral cancer invasion through the Carma3/Bcl10/Malt1 complex. *Int J Oral Sci* 2009; **1**: 105–118.
- 136 Yuecheng Y, Xiaoyan X. Stromal-cell derived factor-1 regulates epithelial ovarian cancer cell invasion by activating matrix metalloproteinase-9 and matrix metalloproteinase-2. *Eur J Cancer Prev* 2007; **16**: 430–435.
- 137 Shen X, Wang S, Wang H, Liang M, Xiao L, Wang Z. The role of SDF-1/CXCR4 axis in ovarian cancer metastasis. *J Huazhong Univ Sci Technolog Med sci* 2009; **29**: 363–367.
- 138 Yang BG, Tanaka T, Jang MH, Bai Z, Hayasaka H, Miyasaka M. Binding of lymphoid chemokines to collagen IV that accumulates in the basal lamina of high endothelial venules: its implications in lymphocyte trafficking. *J Immunol* 2007; **179**: 4376–4382.
- 139 Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, Kleinman ME et al. Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. *Nat Med* 2004; **10**: 858–864.
- 140 Ratajczak MZ, Zuba-Surma E, Kucia M, Reza R, Wojakowski W, Ratajczak J. The pleiotropic effects of the SDF-1-CXCR4 axis in organogenesis, regeneration and tumorigenesis. *Leukemia* 2006; **20**: 1915–1924.
- 141 Romain B, Hachet-Haas M, Rohr S, Brigand C, Galzi JL, Gaub MP et al. Hypoxia differentially regulated CXCR4 and CXCR7 signaling in colon cancer. *Mol Cancer* 2014; **13**: 58.
- 142 Heckmann D, Maier P, Laufs S, Li L, Sleeman JP, Trunk MJ et al. The disparate twins: a comparative study of CXCR4 and CXCR7 in SDF-1alpha-induced gene expression, invasion and chemosensitivity of colon cancer. *Clin Cancer Res* 2014; **20**: 604–616.
- 143 Deutsch AJ, Steinbauer E, Hofmann NA, Strunk D, Gerlza T, Beham-Schmid C et al. Chemokine receptors in gastric MALT lymphoma: loss of CXCR4 and upregulation of CXCR7 is associated with progression to diffuse large B-cell lymphoma. *Mod Pathol* 2013; **26**: 182–194.
- 144 Karin N. The multiple faces of CXCL12 (SDF-1alpha) in the regulation of immunity during health and disease. *J Leuk Biol* 2010; **88**: 463–473.
- 145 Infantino S, Moepes B, Thelen M. Expression and regulation of the orphan receptor RDC1 and its putative ligand in human dendritic and B cells. *J Immunol* 2006; **176**: 2197–2207.
- 146 Kryczek I, Wei S, Keller E, Liu R, Zou W. Stroma-derived factor (SDF-1/CXCL12) and human tumor pathogenesis. *Am J Physiol Cell Physiol* 2007; **292**: C987–C995.
- 147 Gil M, Komorowski MP, Seshadri M, Rokita H, McGray AJ, Opyrchal M et al. CXCL12/CXCR4 blockade by oncolytic virotherapy inhibits ovarian cancer growth by decreasing immunosuppression and targeting cancer-initiating cells. *J Immunol* 2014; **193**: 5327–5337.
- 148 Gil M, Seshadri M, Komorowski MP, Abrams SI, Kozbor D. Targeting CXCL12/CXCR4 signaling with oncolytic virotherapy disrupts tumor vasculature and inhibits breast cancer metastases. *Proc Natl Acad Sci USA* 2013; **110**: E1291–E1300.
- 149 Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci USA* 2013; **110**: 20212–20217.
- 150 Limon-Flores AY, Chacon-Salinas R, Ramos G, Ullrich SE. Mast cells mediate the immune suppression induced by dermal exposure to JP-8 jet fuel. *Toxicol Sci* 2009; **112**: 144–152.
- 151 Sarchio SN, Scolyer RA, Beaugie C, McDonald D, Marsh-Wakefield F, Halliday GM et al. Pharmacologically antagonizing the CXCR4-CXCL12 chemokine pathway with AMD3100 inhibits sunlight-induced skin cancer. *J Invest Dermatol* 2014; **134**: 1091–1100.
- 152 Byrne SN, Sarchio SN. AMD3100 protects from UV-induced skin cancer. *Oncoimmunology* 2014; **3**: e27562.
- 153 Chen Y, Ramjiawan RR, Reiberger T, Ng MR, Hato T, Huang Y et al. CXCR4 inhibition in tumor microenvironment facilitates anti-PD-1 immunotherapy in sorafenib-treated HCC in mice. *Hepatology* 2014; e-pub ahead of print 20 December 2014; doi:10.1002/hep.27665.
- 154 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**: 152–161.
- 155 Durr C, Pfeifer D, Claus R, Schmitt-Graeff A, Gerlach UV, Graeser R et al. CXCL12 mediates immunosuppression in the lymphoma microenvironment after allogeneic transplantation of hematopoietic cells. *Cancer Res* 2010; **70**: 10170–10181.
- 156 Redjal N, Chan JA, Segal RA, Kung AL. CXCR4 inhibition synergizes with cytotoxic chemotherapy in gliomas. *Clin Cancer Res* 2006; **12**: 6765–6771.
- 157 Yoon Y, Liang Z, Zhang X, Choe M, Zhu A, Cho HT et al. CXCR4 antagonist blocks both growth of primary tumor and metastasis of head and neck cancer in xenograft mouse models. *Cancer Res* 2007; **67**: 7518–7524.
- 158 Smith MC, Luker KE, Garbow JR, Prior JL, Jackson E, Piwnicka-Worms D et al. CXCR4 regulates growth of both primary and metastatic breast cancer. *Cancer Res* 2004; **64**: 8604–8612.
- 159 Kajiyama H, Shibata K, Terauchi M, Ino K, Nawa A, Kikkawa F. Involvement of SDF-1alpha/CXCR4 axis in the enhanced peritoneal metastasis of epithelial ovarian carcinoma. *Int J Cancer* 2008; **122**: 91–99.
- 160 Scotton CJ, Wilson JL, Scott K, Stamp G, Wilbanks GD, Fricker S et al. Multiple actions of the chemokine CXCL12 on epithelial tumor cells in human ovarian cancer. *Cancer Res* 2002; **62**: 5930–5938.
- 161 Ray P, Lewin SA, Mihalko LA, Schmidt BT, Luker KE, Luker GD. Noninvasive imaging reveals inhibition of ovarian cancer by targeting CXCL12-CXCR4. *Neoplasia* 2011; **13**: 1152–1161.
- 162 Righi E, Kashiwagi S, Yuan J, Santosuoso M, Leblanc P, Ingraham R et al. CXCL12/CXCR4 blockade induces multimodal antitumor effects that prolong survival in an immunocompetent mouse model of ovarian cancer. *Cancer Res* 2011; **71**: 5522–5534.
- 163 Kawaguchi A, Orba Y, Kimura T, Iha H, Ogata M, Tsuji T et al. Inhibition of the SDF-1alpha-CXCR4 axis by the CXCR4 antagonist AMD3100 suppresses the migration of cultured cells from ATL patients and murine lymphoblastoid cells from HTLV-I tax transgenic mice. *Blood* 2009; **114**: 2961–2968.
- 164 Zeng Z, Shi YX, Samudio IJ, Wang RY, Ling X, Frolova O et al. Targeting the leukemia microenvironment by CXCR4 inhibition overcomes resistance to kinase inhibitors and chemotherapy in AML. *Blood* 2009; **113**: 6215–6224.
- 165 Thiele S, Mungalpara J, Steen A, Rosenkilde MM, Vabeno J. Determination of the binding mode for the cyclopentapeptide CXCR4 antagonist FC131 using a dual approach of ligand modifications and receptor mutagenesis. *Br J Pharmacol* 2014; **171**: 5313–5329.
- 166 Kwong J, Kulbe H, Wong D, Chakravarty P, Balkwill F. An antagonist of the chemokine receptor CXCR4 induces mitotic catastrophe in ovarian cancer cells. *Mol Cancer therapeutics* 2009; **8**: 1893–1905.
- 167 Shaked Y, Henke E, Roodhart JM, Mancuso P, Langenberg MH, Colleoni M et al. Rapid chemotherapy-induced acute endothelial progenitor cell mobilization: implications for antiangiogenic drugs as chemosensitizing agents. *Cancer Cell* 2008; **14**: 263–273.
- 168 Xu L, Duda DG, di Tomaso E, Ancukiewicz M, Chung DC, Lauwers GY et al. Direct evidence that bevacizumab, an anti-VEGF antibody, up-regulates SDF1alpha, CXCR4, CXCL6, and neuropilin 1 in tumors from patients with rectal cancer. *Cancer Res* 2009; **69**: 7905–7910.
- 169 Ratajczak MZ, Jadczyk T, Schneider G, Kakar SS, Kucia M. Induction of a tumor-metastasis-receptive microenvironment as an unwanted and underestimated side effect of treatment by chemotherapy or radiotherapy. *J Ovarian Res* 2013; **6**: 95.

- 170 Salomonsson E, Stacer AC, Ehrlich A, Luker KE, Luker GD. Imaging CXCL12-CXCR4 signaling in ovarian cancer therapy. *PLoS ONE* 2013; **8**: e51500.
- 171 Welschinger R, Liedtke F, Basnett J, Dela Pena A, Juarez JG, Bradstock KF *et al*. Plerixafor (AMD3100) induces prolonged mobilization of acute lymphoblastic leukemia cells and increases the proportion of cycling cells in the blood in mice. *Exp Hematol* 2013; **41**: 293–302 e291.
- 172 Domanska UM, Timmer-Bosscha H, Nagengast WB, Oude Munnink TH, Kruizinga RC, Ananias HJ *et al*. CXCR4 inhibition with AMD3100 sensitizes prostate cancer to docetaxel chemotherapy. *Neoplasia* 2012; **14**: 709–718.
- 173 Hoellenriegel J, Zboralski D, Maasch C, Rosin NY, Wierda WG, Keating MJ *et al*. The Spiegelmer NOX-A12, a novel CXCL12 inhibitor, interferes with chronic lymphocytic leukemia cell motility and causes chemosensitization. *Blood* 2014; **123**: 1032–1039.
- 174 Liu SC, Alomran R, Chernikova SB, Lartey F, Stafford J, Jang T *et al*. Blockade of SDF-1 after irradiation inhibits tumor recurrences of autochthonous brain tumors in rats. *Neuro-oncology* 2014; **16**: 21–28.
- 175 Vater A, Sahlmann J, Kroger N, Zollner 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**: 150–157.
- 176 Roccaro AM, Sacco A, Purschke WG, Moschetta M, Buchner K, Maasch C *et al*. SDF-1 inhibition targets the bone marrow niche for cancer therapy. *Cell Rep* 2014; **9**: 118–128.