

CXCR4 and Cancer

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Abstract The chemokine receptor CXCR4 belongs to the large superfamily of G-protein-coupled receptors, and is directly involved in a number of biological processes including organogenesis, hematopoiesis, and immunity. Recent evidence has highlighted the role of CXCR4 in a variety of diseases including cancer and WHIM syndrome. Expression of CXCR4 in cancer metastasis appears to be due to dysregulation of the receptor leading to enhanced signaling. CXCR4 was also found to be a prognostic marker in various types of cancer including leukemia and breast cancer. These observations reveal that CXCR4 is an important molecule involved in several aspects of cancer progression. The SDF-1-CXCR4 axis is also involved in normal stem cell homing. Interestingly, cancer stem cells also express CXCR4 suggesting that the SDF-1-CXCR4 axis directs their trafficking/metastasis to organs that highly express SDF-1 such as the lymph nodes, lungs, liver, and bones. Here, we review what is currently known regarding the regulation of CXCR4 and how dysregulation contributes to disease progression.

The Chemokine Receptor CXCR4 and Cancer

The human chemokine system currently includes more than 40 chemokines and 18 chemokine receptors (Table 1). Chemokine receptors are defined by their ability to induce directional migration of cells toward a gradient of a chemotactic cytokine (chemotaxis). Chemokine receptors belong to a family of 7 transmembrane domain, G-protein-coupled cell surface receptors (GPCR) and the ligands are classified into four groups (CXC, CC, C, and CX₃C) based on the position of the first two cysteines [1, 2]. Chemokine receptors are present on many different cell types. Initially, these receptors were identified on

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Table 1 Chemokine receptors and ligands

Receptor	Ligand
CXC Chemokine	
CXCR1	GCP-2/CXCL6, IL-8/CXCL8
CXCR2	GRO α,β,γ /CXCL1,2,3, ENA-78/CXCL5, GCP-2/CXCL6, IL-8/CXCL8
CXCR3	MIG/CXCL9, IP-10/CXCL10, I-TAC/CXCL11, BLC/CXCL 13, SLC/CCL21
CXCR4	SDF-1/CXCL12
CXCR5	CXCL13/BLC
CXCR6	CXCL16
CC Chemokine	
CCR1	MIP-1 α /CCL3, RANTES/CCL5, MCP-3/CCL7, MCP-2/CCL8, LD78 β /CCL3L1, HCC-1/CCL14, Lkn-1/CCL15, LEC/CCL16, MPIF-1/CCL23
CCR2	MCP-1/CCL2, MCP-2/CCL8, MCP-3/CCL7, MCP-4/CCL13, LEC/CCL16
CCR3	RANTES/CCL5, MCP-2/CCL8, MCP-3/CCL7, MCP-4/CCL13, eotaxin-1,2,3/CCL11, 24, 26, LD78 β /CCL3L1, Lkn-1/CCL15, MEC/CCL28
CCR4	TARC/CCL17, MDC/CCL22
CCR5	MIP-1 α /CCL3, MIP-1 β /CCL4, RANTES/CCL5, MCP-2/CCL8, LD78 β /CCL3L1, LEC/CCL16
CCR6	LARC/CCL20, β -defensin
CCR7	ELC/CCL19, SLC/CCL21
CCR8	I-309/CCL1
CCR9	TECK/CCL25
CCR10	ILC/CCL27, MEC/CCL28
C Chemokine	
XCR1	SCM-1/XCL1,2
CX₃C Chemokine	
CX ₃ CR1	fractalkine/CX ₃ CL1

leukocytes, where they were found to play an important role in the “homing” of such cells to sites of inflammation [3].

During the past several years, other types of cells (nonhematopoietic) also have been found to express receptors for various chemokines present in their distinct tissue microenvironments. The interactions between such receptors and their respective chemokines are thought to help coordinate the trafficking and organization of cells within various tissue compartments [4, 5].

CXCR4 is one of the most studied chemokine receptors, primarily due to its role as a coreceptor for HIV entry [6] as well as its ability to mediate the metastasis of a variety of cancers including prostate cancer [7–11].

CXCR4 is a 352 amino acid rhodopsin-like GPCR that selectively binds the CXC chemokine stromal cell-derived factor 1 (SDF-1), also known as CXCL12 [1, 12].

In animal models, the lack of either SDF-1 or CXCR4 exhibits an almost identical phenotype of late gestational lethality and defects in B cell lymphopoiesis, bone marrow colonization, and cardiac septum formation [13, 14]. These studies indicated that CXCR4 is essential for development, hematopoiesis, organogenesis, and vascularization [13–19], in addition to functioning as a classical chemokine receptor in adults [5, 19].

There is growing evidence that CXCR4 functions not only in cancer metastasis but it also seems to be involved in the “cancer stem cell” process. The physiologic mechanisms of tissue-specific recruitment features (the “homing” system for normal tissue replacement) also seem functional in cancer cells.

This review will focus on the role of CXCR4 in cancer, particularly in the putative cancer stem cell. We will discuss what is known about the factors involved in receptor expression and regulation, how dysregulation of these pathways may contribute to disease progression, and the potential options for targeted therapy.

Concept of Cancer Stem Cells

The growing evidence shows that quiescent tissue-committed stem cells (TCSCs), cells that are closely related to the development of each organ, may be the origin of cancer development. The concept of cancer stem cells has been postulated by several investigators since it was initially documented by experiments in human leukemias [20]. Stem cells are long-living cells and thus become a potential target for cell damage; they will be subjected to accumulating mutations, which are crucial for the initiation and progression of cancer. Several studies have shown that mutations that occur in normal stem cells can lead to their malignant transformation and tumor initiation [21–23].

A recent study shows that the stem cell origin of cancer was demonstrated in several solid tumors such as brain, breast, and prostate cancers [24–26]. They also are thought to be “tough guys” in response to chemotherapy. Since cancer stem cells are similar to normal stem cells, when they exist in a quiescent state they are relatively resistant to most anticancer drugs which target only dividing cells. Cancer stem cells only represent a subpopulation of a growing tumor. They are capable of initiating metastasis and they regroup (or function as “seeds”) to form new tumors after unsuccessful treatment.

The bottom line is that CXCR4 is expressed in the normal stem cells of different organs/tissues. This may help to explain why some tumors express CXCR4, and why we believe these malignant cells may derive from CXCR4 expressing normal stem cells (Table 2).

Table 2 Examples of tumors expressing CXCR4 that may derive from the normal stem cells which express CXCR4 (Adapted From Ref #9)

Normal cells	Corresponding tumor
Prostate gland epithelial stem cells	Prostate cancer
Hematopoietic stem cells	Leukemias
Neural stem cells	Brain tumors
Mammary gland epithelial stem cells	Breast cancer
Skeletal muscle satellite cells	Rhabdomyosarcoma
Neuroectodermal stem cells	Neuroblastoma
Renal tubular epithelial stem cells	Wilms' tumor
Retina pigment epithelial stem cells	Retinoblastoma
Liver oval stem cells	Hepatoblastoma
Ovarian epithelial stem cells	Ovarian cancer
Cervical epithelial stem cells	Cervical cancer

The Role of CXCR4-SDF-1 Axis Involved in Mobilization, Trafficking, and Homing of Cancer Stem Cells

The SDF-1–CXCR4 axis may influence the biology of tumors. It is believed that the organs that express high SDF-1 (e.g., lymph nodes, lungs, liver, or bones) may direct the metastasis of CXCR4-expressing tumor cells.

Supporting this hypothesis, it has been reported that several cancers expressing CXCR4 (e.g., breast, ovarian, and prostate cancers, rhabdomyosarcoma, and neuroblastoma) metastasize to the bones through the bloodstream in an SDF-1-dependent manner [11, 25, 27–32]. The role of the SDF-1–CXCR4 axis in regulating the trafficking/homing of tumor cell metastasis seems to share some of the molecular mechanisms involved in normal stem cell processes. Seen from this perspective, the mobilization, trafficking, and homing of both cancer and normal stem cells seem to involve multistep processes as described in several studies [9, 33–35] (Fig. 1).

CXCR4 Receptor Expression, Regulation, and Pathway

Interestingly, CXCR4 is expressed in a variety of cancers but its expression in the adjacent normal tissue is rare [11, 27, 36]. This may result from changes that occur within the vasculature or the O₂-carrying capacity of cells, leading to hypoxic conditions during tumor progression [37]. Hypoxia induces the activation of hypoxia inducible factor 1 (HIF-1) which may also promote expression of a number of target genes including CXCR4 [37–40].

This function of HIF-1 was discovered in studies of the tumor suppressor gene, von Hippel Lindau (VHL). Inactivating mutations of VHL, which

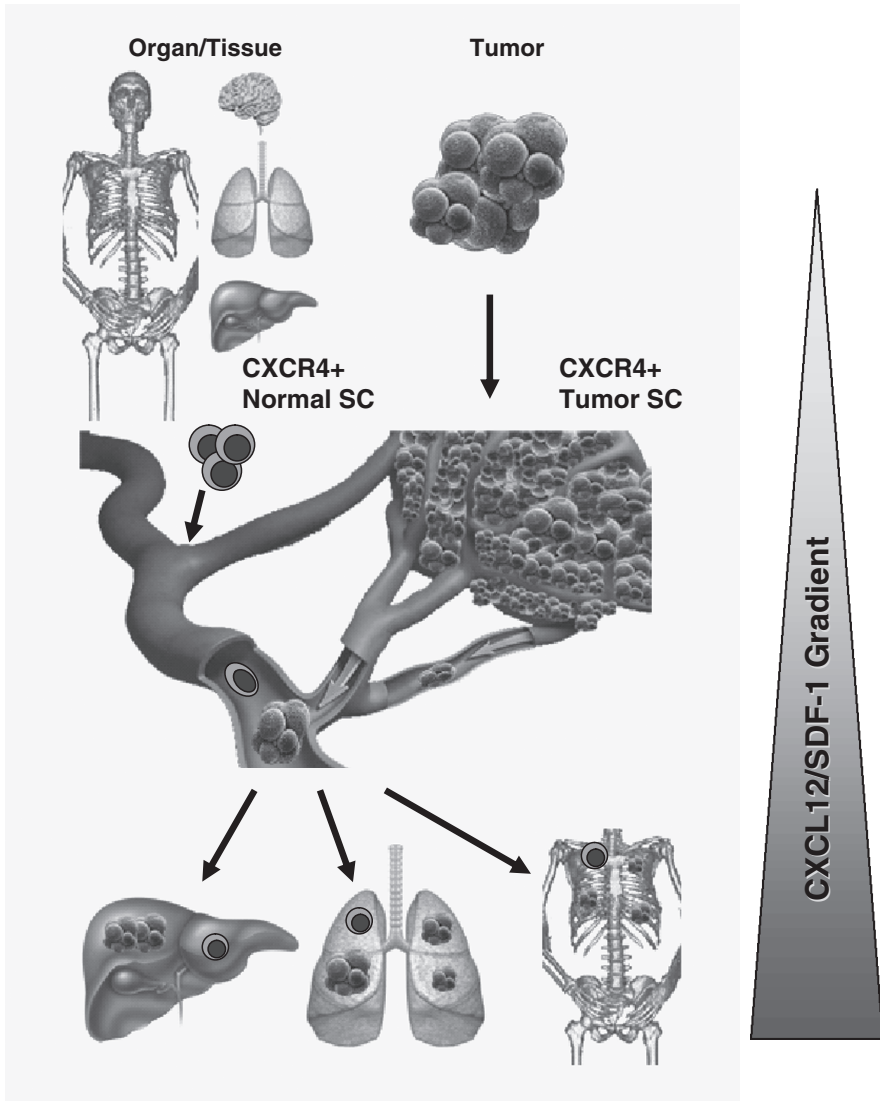


Fig. 1 The role of the SDF-1–CXCR4 axis in migration/circulation of normal stem cells and metastasis of cancer stem cells. Migration of normal stem cells and metastasis of malignant stem cells is a multistep process in which cells (I) leave their stem cell niches (normal stem cells) or primary tumor (cancer stem cells) and enter circulation, (II) arrive at the site of homing (normal stem cells) or metastasis (malignant stem cells) via the peripheral blood or lymph, (III) adhere to the endothelium, (IV) invade tissues, and proliferate and expand at a location that provides a supportive environment for them. We hypothesize that CXCL12/SDF-1 plays a crucial role in this process, chemoattracting CXCR4+ normal or tumor stem cells. Abbreviations: SC stem cell, SDF stromal-derived factor. (Modified from Kucia M., Reza R., Miekus K., et al. (2005) Trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms: Pivotal role of the SDF-1-CXCR4 axis. *Stem Cells*, **23**, 879–94.)

normally targets HIF-1 for degradation, account for the increased CXCR4 expression in renal cell carcinomas [38–40].

The vascular endothelial growth factor (VEGF) [41] and/or activation of nuclear factor kappa B (NF- κ B) [42] also have the ability to increase CXCR4 expression specifically during cancer progression. These genes enhance CXCR4 expression in breast cancer, promoting invasion and metastasis.

Further, it has been shown that oncoproteins also induce CXCR4 expression. These are known as PAX3-FKHR [31, 43] and RET/PTC [44]. The PAX3-FKHR fusion leads to enhanced migration and adhesion of rhabdomyosarcoma cells [31], while RET/PTC-induced expression enhanced the transforming ability of breast cancer cells [44].

Tumor progression, especially in tumor metastasis, is also affected by CXCR4-SDF-1 signaling through the induction of tumor-associated integrin activation and signaling [45]. CXCR4 also stimulates the production of matrix metalloproteases [46–49]. SDF signaling is also able to enhance integrin activity [50–52], enhancing cell adhesion under flow conditions.

If CXCR4 truly mediates metastasis, when tumors enter the blood or lymphatic systems, they would preferentially migrate and adhere to areas with high expression of SDF-1. Breast cancer follows this pattern of metastasis, migrating to lymph nodes, lung, liver, and bone marrow, all of which have high expression of SDF-1 [30, 53]. In vivo, neutralizing antibodies to CXCR4 [30], or silencing CXCR3 by siRNA [54, 55] inhibited the metastasis and growth of breast cancer cells.

Other cancers, such as small cell lung cancer, thyroid, neuroblastoma, hematological, and hepatic malignancies also metastasize to areas with high SDF-1 expression [28, 56–59]. Previous studies have suggested that expression of CXCR4 in hepatocellular carcinoma correlates with local tumor progression, lymphatic and distant metastasis, as well as negatively impacting the 3-year survival rate of these patients [59].

Epigenetic mechanisms that negatively regulate the expression of SDF or CXCR4 may be necessary for tumor metastasis. One example is DNA methylation, a modification typically associated with inactivation of tumor suppressors, and it has been shown that methylation of the SDF promoter in colonic epithelium promotes metastasis of these tumors [60, 61]. Also, the CXCR4 promoter was found to be regulated by DNA methylation in pancreatic cancer, which shows decreasing mRNA and protein levels [62].

Further, the CXCR4 COOH-terminal domain also seems to play a major role in regulating receptors, including epithelial-to-mesenchymal transition (EMT) [63, 64]. Previous studies suggest the C-terminal truncation mutations in the chemokine receptor CXCR4 in warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome are the first examples of aberrant chemokine receptor function causing human disease [63]. It also has been shown that expression of C-tail truncated mutant of CXCR4 in MCF-7 mammary carcinoma cells exhibits a higher growth rate and alters morphology as indicated by EMT [64].

Taken together, CXCR4 seems to control many diverse processes, from development to cancer metastasis. A large amount of work has been generated in delineating potential pathways that mediate specific effects (e.g., leading to metastasis); however, a detailed receptor regulation process has not been well established yet. Understanding the precise mechanisms regulating CXCR4 function at the receptor level may provide new insight into attractive therapeutic targets in this pathway.

Conclusion and Future Directions

The concept of chemokines influencing the metastatic destination is beginning to be understood. The pictures of chemokine receptors expressed by cancer stem cells seem to represent an important aspect of tumorigenesis and metastasis. The expression of CXCR4 in cancer stem cells is likely to be involved in the organ-specific metastasis, that is, prostate cancer metastasizing to the bone. However, even if the overall findings and hypothesis are correct, in the real world, any such therapeutic method (e.g., a CXCR4 antagonist for a prostate cancer patient with bone metastasis) is unlikely to be used alone, but rather used in combination with established chemotherapy protocols.

From the basic science aspect, there is a lot to learn about CXCR4 and its association with cancers (Table 3). CXCR4 involvement in cancer metastasis mechanisms suggests that CXCR4 antagonism may be a potential option for tackling cancer metastasis [65]. Transfecting CXCR4 into a tumor cell greatly enhances its metastatic potential [140]. Therefore, instead of trying to antagonize this receptor, it may be better to modulate CXCR4 expression in tumor cells to prevent metastasis.

Targeting cancer stem cells may offer improvements in therapy in addition to targeting CXCR4, and future studies are likely to include the identification of cancer stem cell specific surface markers for antibody therapy, elucidation of cancer stem cell specific pathways that can be pharmacologically targeted, and evaluation of agents that promote the differentiation of cancer stem cells into progenitors that do not self-renew.

While the role of CXCR4 and cancer stem cells present exciting clinical implications, its widespread acceptance and application to the practice of medicine has yet to occur.

We anticipate that the findings described in this chapter will be identified in additional tumor types, and knowledge of the detailed biology and clinical significance of this experimentally defined population will provide further support to the concept.

Ultimately, focusing research efforts on the role of CXCR4 and cancer stem cell may drive important advances in our understanding of cancer biology and developing potential cures for these devastating diseases.

Table 3 CXCR4 expression in various cancers

Cancer expressing CXCR4	Reference number
Colon Cancer	[66–68]
Breast Cancer	[69–73]
Lung Cancer	[74–80]
Ovarian Cancer	[81–86]
Prostate Cancer	[87–92]
Kidney Cancer	[93–97]
Brain Cancer	[98, 100–105]
Thyroid Cancer	[44, 57, 106, 107]
Liver Cancer	[59]
Pancreatic Cancer	[108–113]
Esophageal Cancer	[114–116]
Cervical Cancer	[117–119]
Oral Cancer	[120–123]
Melanoma	[124–132]
Leukemia	[133–139]

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