



# Involvement of CXCL12/CXCR4 axis in colorectal cancer: a mini-review

Mayara Bocchi<sup>1</sup> · Nathália de Sousa Pereira<sup>1</sup> · Karen Brajão de Oliveira<sup>1,2</sup> · Marla Karine Amarante<sup>1</sup>

Received: 19 January 2023 / Accepted: 19 April 2023 / Published online: 23 May 2023  
© The Author(s), under exclusive licence to Springer Nature B.V. 2023

## Abstract

Migration of metastatic tumor cells is similar to the traffic of leukocytes and has been reported that can be guided by chemokines and their receptors, through the circulation to distant organs. The chemokine CXCL12 and its receptor CXCR4 play an essential role in hematopoietic stem cell homing and the activation of this axis supports malignant events. Binding of CXCL12 to CXCR4 activates signal transduction pathways, with broad effects on chemotaxis, cell proliferation, migration and gene expression. Thus, this axis serves as a bridge for tumor-stromal cell communication, creating a permissive microenvironment for tumor development, survival, angiogenesis and metastasis. Evidence suggests that this axis may be involved in the colorectal cancer (CRC) carcinogenesis. Therefore, we review emerging data and correlations between CXCL12/CXCR4 axis in CRC, the implications for cancer progression and possible therapeutic strategies that exploit this system.

**Keywords** Chemokines · Chemokine receptors · Colorectal cancer · CXCL12 · CXCR4

## Introduction

Cancer is characterized by unregulated proliferation of host cells, arising from alterations in cell physiology, such as: sufficiency in relation to growth factors, insensitivity to growth inhibitors, evasion of apoptosis and the immune system, dysregulation of energy metabolism, genomic instability, phenotypic plasticity, epigenetic reprogramming, tissue invasion and development of metastases [1, 2]. Although the tumor cell represents the main focus in the development of a neoplasm, it is important to consider that the tumor mass is not composed only of neoplastic cells, but of a set of tumor cells, mesenchymal cells and components of the vascular and immune system, which contribute substantially to carcinogenesis, tumor progression and metastasis of transformed cells [3].

Evidence indicates that interactions between tumor cells and stromal cells contribute to tumor initiation and progression. In this process, the role of chemokines and their receptors is highlighted, which can serve as a bridge for tumor-stromal cell communication, creating a permissive microenvironment for tumor growth and metastasis [4], sometimes facilitating tumor dissemination in each of the events of the process, including adherence of tumor cells to the endothelium, extravasation into blood vessels, metastatic colonization, angiogenesis, proliferation and protection against host response through activation of cell survival pathways [5, 6].

Bowel cancer encompasses tumors that start in the part of the large intestine: colon, rectum and anus. It is also known as colon and rectum or colorectal cancer (CRC). This cancer is the third most common cancer type worldwide; in 2020, almost 2 million cases were diagnosed. It is the second most common cause of cancer death, leading to almost 1 million deaths per year [7]. Although environmental and genetic factors play an important role in the pathogenesis of CRC, research suggests the involvement of chemokines and their receptors in the development of colon cancer [8, 9].

Binding of the C-X-C motif chemokine 12 (CXCL12) with its C-X-C motif chemokine receptor 4 (CXCR4) has been associated with several types of malignant neoplasms [10–13]. Studies have demonstrated increased expression of

✉ Marla Karine Amarante  
marla@uel.br

<sup>1</sup> Oncology Laboratory, Department of Pathology, Clinical and Toxicological Analysis, Health Sciences Center, Londrina State University, Londrina, PR, Brazil

<sup>2</sup> Department of Pathological Sciences, Biological Sciences Center, Londrina State University, Londrina, PR, Brazil

CXCR4 during CRC malignancy [14, 15]. However, despite contributing to tumor development and maintenance, the signaling mechanism through CXCR4 may be clinically relevant for CRC patients and represents a potential target for disease-directed therapy [16, 17].

### Chemokines and their receptors

Chemokines are a large family of structurally homologous cytokines responsible for inducing chemotaxis, through binding to a receptor. They are divided into subfamilies according to the number and position of cysteine residues in the N-terminal portion: C, CC, CXC, and CX3C, where C represents the cysteine molecule and X or X3, refer to the number of variable amino acid residues separating these cysteines [18].

Produced by different cell types, both constitutively and after induction stimuli, chemokines exert their effects in an autocrine or paracrine manner, acting via G protein-coupled receptors [19]. In addition to its chemotactic activity, stimulating the migration of immune, endothelial, mesenchymal stem and malignant epithelial cells [20], chemokines have other functions, such as participating in embryonic development, acting in hematopoiesis, angiogenesis, lymphocyte development, cell maturation and directing the movement of mononuclear cells through the blood [21].

Chemokines are also gaining scientific prominence because of their crucial roles in diseases development and pathological processes, such as inflammation, autoimmune and infectious diseases, like in human immunodeficiency virus (HIV) infection and in cancer [5, 6] They are considered key mediators for tumor growth, angiogenesis, metastases and cellular recruitment for the composition of the tumor microenvironment [20].

Chemokines mediate their functions in target cells through their receptors, which are composed of transmembrane G protein-coupled receptors. In general, they are 320 to 380 amino acids in length and show significant sequence homology. In addition, receptors have an N-terminal portion on the outside of the cell surface, 3 intracellular loops, 3 extracellular loops and a C-terminal portion in the cytoplasm [22]. The binding of chemokines to their ligands triggers conformational alterations in the receptor that culminate in the activation of the G protein. In this way, the subunits of this protein dissociate, leading to the activation of several signal transduction pathways [19, 21].

Receptors are classified as CC, CXC, CX3C, or XC according to the subfamily of their ligands, followed by the letter R (receptor) and a number that reflects the order of their discovery [22]. Furthermore, the receptors are divided into two groups: G-protein-coupled chemokine receptors, which act in several signal transduction pathways, and

atypical chemokine receptors, that appear to remove chemokines and contribute to the control of inflammation in a G protein-independent manner [16].

### The CXCL12/CXCR4 axis

Among the chemokines, we can highlight the role of CXCL12 in tumor progression and metastasis. Its gene, *CXCL12*, is located at position 10q11.1 and was first cloned into a bone marrow-derived cell line and later identified as pre-B cell growth stimulating factor (PBSF) [23]. Also called stromal cell-derived factor 1 (SDF-1), this chemokine is constitutively produced in the bone marrow by immature osteoblasts and endothelial cells, as well as by epithelial cells in various organs, such as the lung, liver, adrenal glands and lymph nodes [24].

CXCL12 has six isoforms (CXCL12  $\alpha$  to  $\phi$ ) derived from alternative splicing, with CXCL12 $\alpha$  and CXCL12 $\beta$  being the most widely studied subtypes. The  $\alpha$  isoform is increased in tissue damage but is rapidly degraded in the blood. In addition, it is the main form secreted by bone marrow cells and endothelial cells, found in almost all organs. The  $\beta$  isoform is more resistant to degradation, stimulates angiogenesis and is present in highly vascularized organs such as liver, spleen and kidney [16].

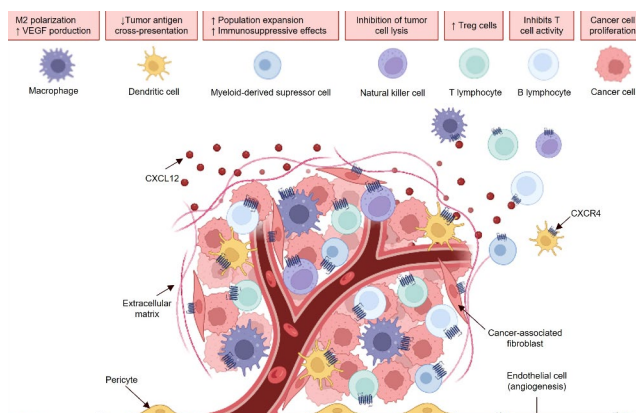
Literature data suggest that CXCL12 acts as a modulator of cell growth and survival by binding to its receptor, CXCR4, playing a key role in the homing of stem and hematopoietic progenitor cells. The gene encoding CXCR4 is located on chromosome 2q2 and is expressed in dendritic cells, naive T cells, natural killer cells and monocytes [25]. In addition, the production of this chemokine in the initial stage of the disease aids in the process of angiogenesis and in the growth of tumor cells, while in more advanced stages, production decreases in order to avoid the recruitment of cytotoxic lymphocytes and increases the metastatic potential of tumor cells [26], being implicated in the spread of malignant tumors from the primary site, transendothelial migration of tumor cells and homing of precursor tumor cells [27]. The expression of CXCR4 in malignant cells indicates that the CXCL12/CXCR4 axis can influence tumor biology and play a key role in directing metastasis of CXCR4+ tumor cells towards organs that express CXCL12 [28].

The CXCL12/CXCR4 interaction was believed to be unique, until the description of another receptor, CXCR7, with a strong affinity for CXCL12 [29]. CXCR7 is part of the G protein-coupled cell surface receptor family and is also associated with tumor cell survival, migration, adhesion, angiogenesis and metastasis [25]. CXCR7-mediated activation of intracellular signals remains controversial since, unlike typical chemokine receptors, CXCR7 does not activate heterotrimeric G proteins [16]. The CXCR7 sequence

presents a small modification and when bound to CXCL12, there is no increase in intracellular  $\text{Ca}^{2+}$  release, an essential step in the recruitment and activation of G proteins [30]. The CXCR7 receptor is reported to be highly expressed in many tumors and tumor-associated blood vessels, including cancers of the liver, colon, pancreas, prostate and lungs [16, 31–33]. In CRC, its role in tumorigenesis probably occurs by means of histone demethylation, through the formation of heterodimers with CXCR4 [34]. Furthermore, overexpression of CXCR7 is significantly correlated with the presence of distant metastasis, advanced TNM stage, reduced overall survival and disease-free survival in patients with CRC [35].

### Actuation of the CXCL12/CXCR4 axis in the CRC

The CXCL12 chemokine acts in cancer biology by two main mechanisms. The first is related to direct autocrine effects, through the activation of signaling pathways that promote tumor cell growth, metastasis and angiogenesis. The second occurs through indirect effects, where high levels of CXCL12 in tumors attract CXCR4+ inflammatory, vascular and stromal cells to the tumor mass. This favorable microenvironment supports tumor growth through the secretion of growth factors, cytokines, chemokines and pro-angiogenic factors, so an indirect effect is that CXCR4+ tumor cells can be recruited to CXCL12-rich mesenchymal stromal niches to initiate metastasis [4], which can be seen in CRC [28]. Overall, a high CXCR4 expression is clearly associated with an advanced stage of the tumor, an increased risk of recurrence and distant metastases and poor overall survival



**Fig. 1** The tumor microenvironment in CRC. The tumor microenvironment includes both the cellular components surrounding the tumor mass such as immune cells, fibroblasts and epithelial cells and the acellular components including the extracellular matrix and blood vessels. Cancer cells release molecules (CXCL12) that modulate the TME and contribute to cancer growth through immune evasion, metastatic niche formation, neoangiogenesis among other functions that contribute to the hallmarks of cancer. “Created with BioRender.com.”

of CRC [13], with an increased risk of death and progression in patients (Figure 1) [17].

The CXCL12/CXCR4 axis can be regulated by epigenetic, transcriptional and post-transcriptional factors. Regulation of CXCL12/CXCR4 expression by promoter hypermethylation is common in cancer and studies show that the *CXCL12* gene modulates metastatic potential, where it controls its own regulation in an autocrine loop [4]. CRC tumor cells can also undergo DNA hypermethylation at the *CXCL12* promoter, resulting in an imbalance in CXCL12/CXCR4 expression. In this way, tumor cells that lack CXCL12 expression but maintain overexpression of CXCR4 can selectively spread to target organs in which CXCL12 is highly secreted [36, 37].

CXCL12 significantly increases several genes associated with angiogenesis in tumor cells, such as the *IL-6* gene [10]. In CRC, IL-6 activates the janus kinase/signal transducer and activator of transcription (JAK/STAT3) to promote tumor initiation and tumor growth. Thus, the IL-6/STAT3 pathway activates target genes to protect tumor cells from apoptosis, promote angiogenesis and drive tumor cell proliferation, cell cycle progression, invasion and metastasis [38].

Studies demonstrate that transcription factors, such as NF- $\kappa$ B, Sp1 and C/EBP- $\beta$  can be activated through mitogen-activated protein kinase (MAPK) pathways in CRC cells [39]. Tung et al. [40] proposed a relationship between this signal transduction pathway, the chemokine CXCL12 and the expression of intercellular adhesion molecule-1 (ICAM-1). According to the authors, CXCL12 induces extracellular signal-regulated kinase (ERK) phosphorylation, c-Jun N-terminal kinase (JNK) and p38, which consequently activates NF- $\kappa$ B, Sp1 and C/EBP- $\beta$ , leading to their binding to the respective sites on the *ICAM-1* promoter, thus resulting in the transcriptional activation of ICAM-1, facilitating the adhesion of cancer cells to the vascular endothelium and later the promotion of metastases.

The increase in NF- $\kappa$ B mediated by the activation of the MAPK pathway can also occur by stimulation of an external factor, such as visfatin, an adipokine produced by adipose tissue. Huang et al. [41] suggest that visfatin induces the expression of CXCL12 through the activation of  $\beta$ 1 integrin, the ERK and p38 intracellular signaling cascades, and the NF- $\kappa$ B transcription factors and activator protein 1 (AP-1), thus contributing to the progression of CRC. In addition, lipopolysaccharides (LPS), normally produced by the microbiota, also use NF- $\kappa$ B signaling to induce CXCR4 expression in tumor cells, promoting epithelial-mesenchymal transition (EMT) and metastasis in the CRC [39, 42].

A study by Hu et al. [43] demonstrated a cross-relationship between the CXCL12/CXCR4 and Wnt/ $\beta$ -catenin axis in the CRC, where the CXCR4 receptor could aid in disease

progression, invasion and the EMT through the activation of this signaling pathway. Constitutive activation of the Wnt/ $\beta$ -catenin pathway in CRC can occur through aberrant secretion of Wnt factors or a mutation in the *adenomatous polyposis coli (APC)* gene [44].

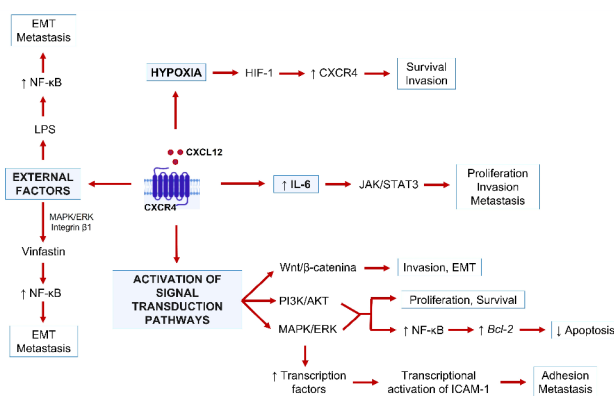
Activation of CXCL12 indirectly exerts anti-apoptotic effects on tumor cells. The CXCL12/CXCR4 axis activates serine-threonine kinase (AKT) and ERK, leading to the accumulation of NF- $\kappa$ B. Accumulation of this transcription factor can suppress apoptotic signaling. In addition, CXCL12 can suppress tumor cell apoptosis by inducing the MAPK-ERK and PI3K pathways, which inactivate the pro-apoptotic protein Bcl-2-associated cell death agonist (BAD), leading to upregulation of the anti-apoptotic gene *Bcl-2* [25, 45].

A hypoxic tumor microenvironment also favors tumor progression during carcinogenesis through upregulation of CXCR4 expression in tumor cells by hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor that responds to tissue oxygen concentrations. Thus, in hypoxic regions of expanding tumors, CXCR4 levels can be increased to facilitate tumor survival and invasion [14, 46].

Figure 2 presents the main mechanisms of action of the CXCL12/CXCR4 axis in the CRC.

## Therapeutic strategies targeting the CXCL12/CXCR4 axis in CRC

This axis is directly involved in the progression of cancer, which, therefore, have an important role in the signaling network, attracting great interest on the part of researchers in exploring therapeutic measures for this target. Thus, studies are seeking inhibitory or antagonist molecules of CXCR4



**Fig. 2** CXCL12/CXCR4 signaling pathway. *Bcl-2*— anti-apoptotic gene; EMT – Epithelial-to-mesenchymal transition; MAPK – mitogen-activated protein kinase; ERK – extracellular signal-regulated kinase; PI3K – phosphatidylinositol-3-kinase; AKT - serine-threonine kinase; JAK/STAT – Janus kinase /signal transducer and activator of transcription; IL-6 – interleukin 6; ICAM-1 – Intercellular Adhesion Molecule 1; NF- $\kappa$ B – nuclear factor kappa B; LPS – Lipopolysaccharide; HIF-1 – hypoxia-inducible factor 1

and CXCL12 that can be used in the treatment of various types of tumors, including CRC [16, 47].

The first therapy targeted at CXCR4 was AMD3100 (Plerixafor), which acts as an antagonist by binding to the CXCR4 receptor, preventing the conformational change necessary to activate intracellular kinases [48]. In addition, its mechanism of action may be related to the mobilization of CD34+ hematopoietic progenitor cells (HPCs), an increase in circulating neutrophils, lymphocytes and monocytes, a reduction in myeloid-derived suppressor cells and increased infiltration of cytotoxic T cells into tumors [47]. Because of these functions, its use was cleared by the Food and Drug Administration (FDA) in 2008 to mobilize HPCs cells for autologous transplantation in patients with non-Hodgkin lymphoma and multiple myeloma [49].

Recent studies have shown that AMD3100 can inhibit tumor growth and metastasis, in addition to acting as a potent immunomodulator to enhance antitumor immune responses and prevent the development of a multifaceted immunosuppressive intratumoral microenvironment [50]. Fearon, Janowitz [51] showed that infusion of AMD3100 in patients with CRC for only 1 week induced intratumoral immune responses that involved multiple mediators and cells of both innate and adaptive immune responses. According to the authors, inhibition of CXCR4 by AMD3100 in patients with CRC allowed their pre-existing anticancer immune responses to overcome intratumoral immunosuppression mediated by CXCL12, through increased expression of genes whose products mediate cytotoxicity by CD8+ T cells, that correlate with decreased expression of genes characteristic of tumor cells. Biasci et al. [52] also demonstrate that continuous administration of AMD3100 promotes an integrated immune response in metastatic lesions of patients with CRC.

Another drug under clinical study is LY2510924, which also acts as a potent and selective antagonist of CXCR4 [53]. LY2510924 showed dose-dependent inhibition of tumor growth in human xenograft models developed with non-Hodgkin's lymphoma, renal cell carcinoma, lung cancer cells and CRC expressing functional CXCR4. Furthermore, its mechanism of action involves the inhibition of the CXCL12/CXCR4 interaction, with consequent blocking of signaling [54]. In addition, several clinical studies show that the administration of LY2510924 was associated with a significant increase in CD34+ HSCs and leukocytes in circulation [55, 56].

The CXCL12 chemokine has also been studied as a possible therapeutic target in different types of tumors, including CRC. CXCL12 acts as a communication bridge between tumor cells and their environment and may confer resistance to *checkpoint* inhibitors by excluding T cells in preclinical models. Studies show that the use of molecules

that interfere with the mechanisms of failure of cytotoxic T cells to physically reach tumor cells can support combined cancer immunotherapy treatments [57, 58].

Evidence indicates that inactivation of CXCL12 by Olaptesed Pegol (NOX-A12) induces alterations in the tumor microenvironment of patients with CRC and pancreatic cancer, making tumors more susceptible to immuno-oncological approaches, such as checkpoint inhibition by anti-PD-1. NOX-A12 is an L-configured aptamer (Spiegelmer) that binds to CXCL12 with high affinity and specificity, blocking the CXCL12/CXCR4 axis. Thus, inhibition of CXCL12 leads to an increase in the infiltration of T cells and natural killer (NK) cells into the tumor [58, 59].

A phase I/II clinical trial (NCT03168139) evaluated the effects of a combination treatment with NOX-A12 and anti-PD-1 in patients with later-line CRC and pancreatic ductal adenocarcinoma [60]. According to the authors, the new approach of specifically inhibiting CXCL12 through a Spiegelmer showed activity alone and in combination with anti-PD-1 in these patients, where the mechanisms of NOX-A12-mediated transformation of the tumor immune microenvironment included the migration of T and NK cells into the tumor.

New molecules targeting the CXCL12/CXCR4 axis have been proposed as possible therapies for CRC. D'Alterio et al. [61] demonstrated in a preclinical trial that the newly developed CXCR4 antagonist, Peptide R (Pep R) is able to improve the efficacy of standard CRC therapy targeting cell growth and mesenchymal transition, through inactivation of CXCR4.

Therapeutic strategies have focused on the potential of CXCR4 antagonists to enhance the cytotoxic effect of chemotherapy and immunotherapy. Furthermore, future therapies may also involve genome editing technologies to remove harmful “driver mutations” and insert “preventive mutations” on the CXCL12/CXCR4 axis [16].

## Conclusion

The CXCL12/CXCR4 plays an important role in the development of several types of malignant neoplasms. Activation of this axis results in the induction of signal transduction pathways, with effects on chemotaxis, cell migration and gene expression. In CRC, increased expression of this axis leads to tumor progression and the development of metastases, with unfavorable disease progression and poor patient survival.

Preclinical and clinical studies have been carried out in order to study several drugs that can inhibit CXCL12/CXCR4 and used in combination with chemotherapy or immunotherapy for the treatment of CRC. In addition, the

development of new research involving genome editing technologies may also represent a future strategy, allowing a more effective therapeutic targeting against the disease.

**Acknowledgements** The authors are grateful for Brazilian Coordination of Superior Level Staff Improvement (CAPES), for the scholarship granted to MB.

**Authors' Contributions** Conceptualization: [Mayara Bocchi], [Nathália de Sousa Pereira], [Karen Brajão de Oliveira], [Marla Karine Amarante]; Literature search, data analysis and manuscript draft: [Mayara Bocchi]; Critical revision: [Nathália de Sousa Pereira], [Karen Brajão de Oliveira], [Marla Karine Amarante].

**Funding** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Data Availability** Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## Declarations

**Competing Interests** The authors have no conflicts of interest to declare that are relevant to the content discussed in this work.

**Ethical approval** Not applicable.

**Consent to participate** All authors have consented to participate of the manuscript production.

**Consent for publication** All authors have read and approved the manuscript for publication.

## References

- Hanahan D (2022) Hallmarks of Cancer: New Dimensions. *Cancer Discov* 12(1):31–46. <https://doi.org/10.1158/2159-8290.cd-21-1059>
- Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144(5):646–674. <https://doi.org/10.1016/j.cell.2011.02.013>
- Kerkar SP, Restifo NP (2012) Cellular constituents of Immune escape within the Tumor Microenvironment. *Cancer Res* 72(13):3125–3130. <https://doi.org/10.1158/0008-5472.can-11-4094>
- Guo F, Wang Y, Liu J, Mok SC, Xue F, Zhang W (2016) CXCL12/CXCR4: a symbiotic bridge linking cancer cells and their stromal neighbors in oncogenic communication networks. *Oncogene* 35(7):816–826. <https://doi.org/10.1038/onc.2015.139>
- Singh S, Sadanandam A, Singh R (2007) Chemokines in tumor angiogenesis and metastasis. *Cancer Metastasis Rev* 26(3):453–467. <https://doi.org/10.1007/s10555-007-9068-9>
- Kakinuma T, Hwang ST (2006) Chemokines, chemokine receptors, and cancer metastasis. *J Leukoc Biol* 79(4):639–651. <https://doi.org/10.1189/jlb.1105633>
- IARC: Colorectal Cancer Awareness Month 2022 (2022) Accessed
- Zou Q, Lei X, Xu A, Li Z, He Q, Huang X et al (2022) Chemokines in progression, chemoresistance, diagnosis, and prognosis of colorectal cancer. *Front Immunol* 13:724139. <https://doi.org/10.3389/fimmu.2022.724139>

9. Braoudaki M, Ahmad MS, Mustafaov D, Seriah S, Siddiqui MN, Siddiqui SS (2022) Chemokines and chemokine receptors in colorectal cancer; multifarious roles and clinical impact. *Sem Cancer Biol* 86(Pt 2):436–449. <https://doi.org/10.1016/j.semcancer.2022.06.002>
10. Li M, Lu Y, Xu Y, Wang J, Zhang C, Du Y et al (2018) Horizontal transfer of exosomal CXCR4 promotes murine hepatocarcinoma cell migration, invasion and lymphangiogenesis. *Gene* 676:101–109. <https://doi.org/10.1016/j.gene.2018.07.018>
11. Mushtaq M, Jensen L, Davidsson S, Grygoruk OV, Andrén O, Kashuba V et al (2018) The MRPS18-2 protein levels correlate with prostate tumor progression and it induces CXCR4-dependent migration of cancer cells. *Sci Rep* 8(1):2268. <https://doi.org/10.1038/s41598-018-20765-8>
12. Truong D, Fiorelli R, Barrientos ES, Melendez EL, Sanai N, Mehta S et al (2019) A three-dimensional (3D) organotypic microfluidic model for glioma stem cells – vascular interactions. *Biomaterials* 198:63–77. <https://doi.org/10.1016/j.biomaterials.2018.07.048>
13. Zielińska KA, Katanaev VL (2020) The signaling duo CXCL12 and CXCR4: chemokine fuel for breast Cancer tumorigenesis. *Cancers* 12(10):3071
14. Yohuantari N, Heriyanto DS, Hutajulu SH, Kurnianda J, Ghozali A (2018) Clinicopathologic significance of CXCL12 and CXCR4 expressions in patients with colorectal Cancer. *Gastroenterol Res Pract* 2018:9613185. <https://doi.org/10.1155/2018/9613185>
15. Zhou Y, Cao H-B, Li W-J, Zhao L (2018) The CXCL12 (SDF-1)/CXCR4 chemokine axis: oncogenic properties, molecular targeting, and synthetic and natural product CXCR4 inhibitors for cancer therapy. *Chin J Nat Med* 16(11):801–810. [https://doi.org/10.1016/S1875-5364\(18\)30122-5](https://doi.org/10.1016/S1875-5364(18)30122-5)
16. Khare T, Bissonnette M, Khare S (2021) CXCL12-CXCR4/CXCR7 Axis in Colorectal Cancer: therapeutic target in preclinical and clinical studies. *Int J Mol Sci* 22(14):7371
17. Ottaiano A, Scala S, Normanno N, Botti G, Tatangelo F, Di Mauro A et al (2020) Prognostic and predictive role of CXC chemokine receptor 4 in metastatic colorectal Cancer patients. *Appl Immunohistochem Mol Morphology* 28(10):755–760. <https://doi.org/10.1097/pai.0000000000000828>
18. Miller MC, Mayo KH (2017) Chemokines from a structural perspective. *Int J Mol Sci* 18(10):2088
19. Bar-Shavit R, Maoz M, Kancharla A, Nag JK, Agranovich D, Grisaru-Granovsky S et al (2016) G protein-coupled receptors in Cancer. *Int J Mol Sci* 17(8):1320
20. Bhusal RP, Foster SR, Stone MJ (2020) Structural basis of chemokine and receptor interactions: key regulators of leukocyte recruitment in inflammatory responses. *Protein Sci* 29(2):420–432. <https://doi.org/10.1002/pro.3744>
21. Hughes CE, Nibbs RJB (2018) A guide to chemokines and their receptors. *FEBS J* 285(16):2944–2971. <https://doi.org/10.1111/febs.14466>
22. Lacalle RA, Blanco R, Carmona-Rodríguez L, Martín-Leal A, Mira E, Mañes S (2017) Chapter five - chemokine receptor signaling and the Hallmarks of Cancer. In: Galluzzi L (ed) *International Review of Cell and Molecular Biology*. Academic Press, pp 181–244
23. Shirozu M, Nakano T, Inazawa J, Tashiro K, Tada H, Shinohara T et al (1995) Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene. *Genomics* 28(3):495–500. <https://doi.org/10.1006/geno.1995.1180>
24. Janssens R, Struyf S, Proost P (2018) The unique structural and functional features of CXCL12. *Cell Mol Immunol* 15(4):299–311. <https://doi.org/10.1038/emi.2017.107>
25. Shi Y, Riese DJ, Shen J (2020) The role of the CXCL12/CXCR4/CXCR7 Chemokine Axis in Cancer. *Front Pharmacol* 11. <https://doi.org/10.3389/fphar.2020.574667>
26. Goïta AA, Guenot D (2022) Colorectal Cancer: the contribution of CXCL12 and its receptors CXCR4 and CXCR7. *Cancers* 14(7):1810
27. Santagata S, Ieranò C, Trotta AM, Capiluongo A, Auletta F, Guardascione G et al (2021) CXCR4 and CXCR7 signaling pathways: a focus on the Cross-Talk between Cancer cells and Tumor Microenvironment. *Front Oncol* 11. <https://doi.org/10.3389/fonc.2021.591386>
28. Teicher BA, Fricker SP (2010) CXCL12 (SDF-1)/CXCR4 pathway in Cancer. *Clin Cancer Res* 16(11):2927–2931. <https://doi.org/10.1158/1078-0432.ccr-09-2329>
29. Balabanian K, Lagane B, Infantino S, Chow KY, Harriague J, Moepps B et al (2005) The chemokine SDF-1/CXCL12 binds to and signals through the orphan receptor RDC1 in T lymphocytes. *J Biol Chem* 280(42):35760–35766. <https://doi.org/10.1074/jbc.M508234200>
30. Wang C, Chen W, Shen J (2018) CXCR7 targeting and its Major Disease Relevance. *Front Pharmacol* 9. <https://doi.org/10.3389/fphar.2018.00641>
31. Gentilini A, Caligiuri A, Raggi C, Rombouts K, Pinzani M, Lori G et al (2019) CXCR7 contributes to the aggressive phenotype of cholangiocarcinoma cells. *Biochimica et Biophysica Acta (BBA) - molecular basis of Disease*. 1865(9):2246–2256. <https://doi.org/10.1016/j.bbadis.2019.04.020>
32. Li X, Wang X, Li Z, Zhang Z, Zhang Y (2019) Chemokine receptor 7 targets the vascular endothelial growth factor via the AKT/ERK pathway to regulate angiogenesis in colon cancer. *Cancer Med* 8(11):5327–5340. <https://doi.org/10.1002/cam4.2426>
33. Lounsbury N (2020) Advances in CXCR7 modulators. *Pharmaceuticals* 13(2):33
34. Song Z-Y, Wang F, Cui S-X, Gao Z-H, Qu X-J (2019) CXCR7/CXCR4 heterodimer-induced histone demethylation: a new mechanism of colorectal tumorigenesis. *Oncogene* 38(9):1560–1575. <https://doi.org/10.1038/s41388-018-0519-2>
35. Zhao Q, Zhang P, Qin G, Ren F, Zheng Y, Qiao Y et al (2018) Role of CXCR7 as a common predictor for prognosis in solid tumors: a Meta-analysis. *J Cancer* 9(17):3138–3148. <https://doi.org/10.7150/jca.25377>
36. Wendt MK, Johanesen PA, Kang-Decker N, Binion DG, Shah V, Dwinell MB (2006) Silencing of epithelial CXCL12 expression by DNA hypermethylation promotes colonic carcinoma metastasis. *Oncogene* 25(36):4986–4997. <https://doi.org/10.1038/sj.onc.1209505>
37. Zhou W, Jiang Z, Liu N, Xu F, Wen P, Liu Y et al (2009) Down-regulation of CXCL12 mRNA expression by promoter hypermethylation and its association with metastatic progression in human breast carcinomas. *J Cancer Res Clin Oncol* 135(1):91–102. <https://doi.org/10.1007/s00432-008-0435-x>
38. Lin Y, He Z, Ye J, Liu Z, She X, Gao X et al (2020) Progress in understanding the IL-6/STAT3 pathway in Colorectal Cancer. *OncoTargets and therapy* 13:13023–13032. <https://doi.org/10.2147/ott.s278013>
39. Tian X, Xie G, Xiao H, Ding F, Bao W, Zhang M (2019) CXCR4 knockdown prevents inflammatory cytokine expression in macrophages by suppressing activation of MAPK and NF-κB signaling pathways. *Cell & Bioscience* 9(1):55. <https://doi.org/10.1186/s13578-019-0315-x>
40. Tung S-Y, Chang S-F, Chou M-H, Huang W-S, Hsieh Y-Y, Shen C-H et al (2012) CXC chemokine ligand 12/Stromal cell-derived factor-1 regulates cell adhesion in human colon cancer cells by induction of intercellular adhesion molecule-1. *J Biomed Sci* 19(1):91. <https://doi.org/10.1186/1423-0127-19-91>
41. Huang W-S, Chen C-N, Sze C-I, Teng C-C (2013) Visfatin induces stromal cell-derived factor-1 expression by β1 integrin signaling in colorectal cancer cells. *J Cell Physiol* 228(5):1017–1024. <https://doi.org/10.1002/jcp.24248>

42. Liu W-T, Jing Y-Y, Yan F, Han Z-P, Lai F-B, Zeng J-X et al (2017) LPS-induced CXCR4-dependent migratory properties and a mesenchymal-like phenotype of colorectal cancer cells. *Cell Adhes Migr* 11(1):13–23. <https://doi.org/10.1080/19336918.2015.1134404>
43. Hu T-h, Yao Y, Yu S, Han L-l, Wang W-j, Guo H et al (2014) SDF-1/CXCR4 promotes epithelial–mesenchymal transition and progression of colorectal cancer by activation of the Wnt/ $\beta$ -catenin signaling pathway. *Cancer Lett* 354(2):417–426. <https://doi.org/10.1016/j.canlet.2014.08.012>
44. Bian J, Dannappel M, Wan C, Firestein R (2020) Transcriptional regulation of Wnt/ $\beta$ -Catenin pathway in Colorectal Cancer. *Cells* 9(9):2125
45. Peng C, Ouyang Y, Lu N, Li N (2020) The NF- $\kappa$ B signaling pathway, the Microbiota, and gastrointestinal tumorigenesis: recent advances. *Front Immunol* 11. <https://doi.org/10.3389/fimmu.2020.01387>
46. Romain B, Hachet-Haas M, Rohr S, Brigand C, Galzi J-L, Gaub M-P et al (2014) Hypoxia differentially regulated CXCR4 and CXCR7 signaling in colon cancer. *Mol Cancer* 13(1):58. <https://doi.org/10.1186/1476-4598-13-58>
47. Wang J, Tannous BA, Poznansky MC, Chen H (2020) CXCR4 antagonist AMD3100 (plerixafor): from an impurity to a therapeutic agent. *Pharmacol Res* 159:105010. <https://doi.org/10.1016/j.phrs.2020.105010>
48. De Clercq E (2015) AMD3100/CXCR4 inhibitor. *Front Immunol* 6. <https://doi.org/10.3389/fimmu.2015.00276>
49. Brave M, Farrell A, Ching Lin S, Ocheltree T, Pope Miksinski S, Lee SL et al (2010) FDA Review Summary: Mozobil in Combination with Granulocyte colony-stimulating factor to mobilize hematopoietic stem cells to the Peripheral blood for Collection and subsequent autologous transplantation. *Oncology* 78(3–4):282–288. <https://doi.org/10.1159/000315736>
50. Liu Z, Wang J, Chen H (2021) CXCR4 antagonist AMD3100 (Plerixafor) modulates Immune responses in the Tumor Microenvironment. *Int J Cancer Clin Res* 8(1). <https://doi.org/10.23937/2378-3419/1410144>
51. Fearon DT, Janowitz T (2021) AMD3100/Plerixafor overcomes immune inhibition by the CXCL12–KRT19 coating on pancreatic and colorectal cancer cells. *Br J Cancer* 125(2):149–151. <https://doi.org/10.1038/s41416-021-01315-y>
52. Biasci D, Smoragiewicz M, Connell CM, Wang Z, Gao Y, Thaventhiran JED et al (2020) CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. *Proceedings of the National Academy of Sciences*. ;117(46):28960–70. doi: <https://doi.org/10.1073/pnas.2013644117>
53. O'Hara MH, Messersmith W, Kindler H, Zhang W, Pitou C, Szpurka AM et al (2020) Safety and Pharmacokinetics of CXCR4 peptide antagonist, LY2510924, in combination with Durvalumab in Advanced Refractory Solid Tumors. *J Pancreat Cancer* 6(1):21–31. <https://doi.org/10.1089/pancan.2019.0018>
54. Peng S-B, Zhang X, Paul D, Kays LM, Gough W, Stewart J et al (2015) Identification of LY2510924, a Novel cyclic peptide CXCR4 antagonist that exhibits Antitumor Activities in solid tumor and breast Cancer metastatic models. *Mol Cancer Ther* 14(2):480–490. <https://doi.org/10.1158/1535-7163.mct-14-0850>
55. Peng S-B, Van Horn RD, Yin T, Brown RM, Roell WC, Obungu VH et al (2017) Distinct mobilization of leukocytes and hematopoietic stem cells by CXCR4 peptide antagonist LY2510924 and monoclonal antibody LY2624587. *Oncotarget*. ; 8(55)
56. Salgia R, Stille JR, Weaver RW, McCleod M, Hamid O, Polzer J et al (2017) A randomized phase II study of LY2510924 and carboplatin/etoposide versus carboplatin/etoposide in extensive-disease small cell lung cancer. *Lung cancer (Amsterdam Netherlands)* 105:7–13. <https://doi.org/10.1016/j.lungcan.2016.12.020>
57. Sharma P, Allison JP (2015) The future of immune checkpoint therapy. *Science* 348(6230):56–61. <https://doi.org/10.1126/science.aaa8172>
58. Zboralski D, Hoehlig K, Eulberg D, Frömming A, Vater A (2017) Increasing tumor-infiltrating T cells through inhibition of CXCL12 with NOX-A12 synergizes with PD-1 blockade. *Cancer Immunol Res* 5(11):950–956. <https://doi.org/10.1158/2326-6066.cir-16-0303>
59. Vater A, Klussmann S (2015) Turning mirror-image oligonucleotides into drugs: the evolution of Spiegelmer® therapeutics. *Drug Discovery Today* 20(1):147–155. <https://doi.org/10.1016/j.drudis.2014.09.004>
60. Suarez-Carmona M, Williams A, Schreiber J, Hohmann N, Pruefer U, Krauss J et al (2021) Combined inhibition of CXCL12 and PD-1 in MSS colorectal and pancreatic cancer: modulation of the microenvironment and clinical effects. *J Immunother Cancer* 9(10):e002505. <https://doi.org/10.1136/jitc-2021-002505>
61. D'Alterio C, Zannetti A, Trotta AM, Ieranò C, Napolitano M, Rea G et al (2020) New CXCR4 antagonist peptide R (pep R) improves Standard Therapy in Colorectal Cancer. *Cancers* 12(7):1952

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.