Seminars in Cancer Biology 86 (2022) 697–708

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Epigenetic regulation of CXCR4 signaling in cancer pathogenesis and progression

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ARTICLE INFO

Keywords:
CXCR
SDF-1/CXCL12
Epigenetic
Non-coding RNA
Methylation/acetylation

ABSTRACT

Signaling involving chemokine receptor CXCR4 and its ligand SDF-1/CXL12 has been investigated for many years for its possible role in cancer progression and pathogenesis. Evidence emerging from clinical studies in recent years has further established diagnostic as well as prognostic importance of CXCR4 signaling. CXCR4 and SDF-1 are routinely reported to be elevated in tumors, distant metastases, which correlates with poor survival of patients. These findings have kindled interest in the mechanisms that regulate CXCR4/SDF-1 expression. Of note, there is a particular interest in the epigenetic regulation of CXCR4 signaling that may be responsible for upregulated CXCR4 in primary as well as metastatic cancers. This review first lists the clinical evidence supporting CXCR4 signaling as putative cancer diagnostic and/or prognostic biomarker, followed by a discussion on reported epigenetic mechanisms that affect CXCR4 expression. These mechanisms include regulation by non-coding RNAs, such as, microRNAs, long non-coding RNAs and circular RNAs. Additionally, we also discuss the regulation of CXCR4 expression through methylation and acetylation. Better understanding and appreciation of epigenetic regulation of CXCR4 signaling can invariably lead to identification of novel therapeutic targets as well as therapies to regulate this oncogenic signaling.

1. Introduction: receptor CXCR4

The Chemokine receptor, C-X-C chemokine receptor 4 (CXCR4) is a G-protein-coupled receptor (GPCR) [1], that is also known by its other names fusin/LESTR and cluster of differentiation-184 (CD184) [2,3]. The most well-characterized ligand that binds and activates CXCR4 is stromal cell-derived factor-1 (SDF-1) [4]. Ligand SDF-1 is also known by its other name, CXCL12 [5]. For many years, SDF-1 was believed to be the exclusive ligand for CXCR4 before ubiquitin was reported as another legitimate ligand for CXCR4 [6]. Even though the two ligands activate CXCR4, leading to similar activation of downstream signaling, there are subtle differences as well, such as the relatively weaker chemotactic activity in case of ubiquitin-activated CXCR4 [7]. Additionally, the cytokine MIF (macrophage migration inhibitory factor) has also been suggested as a ligand for CXCR4 [8]. Thus, CXCR4 can be activated by a cytokine (MIF), a chemokine (SDF-1) as well as a regulatory protein, ubiquitin. Chemokines are a sub-class of cytokines, also referred to as chemotactic cytokines, and, once secreted, they serve as chemo-attractants inducing directional movement of different cell types, including many different immune cells. The important role of both cytokines and chemokines in cancer pathogenesis has been recognized [9,10], in addition to their role in many other diseases as well [11,12], which is primarily because of their profound effect on inflammation and immune responses [9,11,13,14].

CXCR4 activates G protein-dependent signaling pathways, such as, AKT, PI3K, mTOR and EGFR [15,16] as well as G protein-independent signaling pathways, that include, JAK/STAT, p53 MAPK and ERK [1,15]. Under normal conditions, CXCR4 signaling plays a role in

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https://doi.org/10.1016/j.semcancer.2022.03.019
Received 1 February 2022; Received in revised form 18 March 2022; Accepted 21 March 2022
Available online 26 March 2022

embryogenesis, tissue repair, hematopoiesis, organogenesis and immune response [1,17]. Normal cells express little to no CXCR4; however, dysregulated and aberrant CXCR4 expression has been observed and reported in a plethora of tumors [18,19], with serious consequences on cancer progression, especially, cancer cell differentiation, proliferation, invasion, metastasis and angiogenesis [18,20,21]. In this article, the mechanisms of CXCR4 epigenetic dysregulation will be reviewed which could, in turn, affect the influence of CXCR4 signaling on cancer progression and prognosis.

2. CXCR4 signaling in cancer

The GPCR family of proteins, to which receptor CXCR4 belongs, is the largest class of integral membrane proteins [22]. Upon binding of their cognitive ligand, GPCRs are activated via rearrangement of transmembrane helices [22]. The early interest in CXCR4 signaling was related to its identification as the receptor needed for the entry of human immunodeficiency virus-1 (HIV-1) into T-cells [23,24]. The realization that CXCR4 signaling is critically involved in cancer aggressiveness, has fueled the interest in elucidating the various mechanisms by which it influences cancer progression.

2.1. CXCR4 effect on cancer cell proliferation, invasion and metastasis

The ability of cancer cells to proliferate, followed by invasion and metastasis, is central to their propagation and spread. It is, therefore, not surprising that numerous studies have documented a role of CXCR4 signaling in these fundamental processes associated with cancer progression. It is beyond the scope of this article to provide a detailed overview of this topic. The topic has been reviewed extensively [17, 25–31] and we provide only an overview here before discussing the clinical manifestations of CXCR4 in human cancer patients in the next section.

Receptor CXCR4 plays an important role in the induction of cancer proliferation, which often requires activation of cellular signaling such as MAPK or PI3K/Akt signaling pathways, among many others [15,21]. Similarly, overexpression of CXCR4 has been linked to increased invasion and migration, through regulation of multiple pathways [16,32, 33]. Further, angiogenesis is another important phenomenon exhibited by cancer cells. Angiogenesis through CXCR4 activation, in cancer cells, is triggered by platelet-secreted SDF-1, as well as VEGF [4]. As CXCR4 has an associated function in tissue regeneration, it was observed that the SDF-1 is released upon tissue damage [4]. Specifically, platelets in the blood release SDF-1 when a blood vessel is injured, and cancer cells utilize this pathway to trigger angiogenesis. Once released into the microenvironment, SDF-1 activates MMP-9 and soluble kit-ligand release (sKitL). Not only does sKitL has positive feedback on SDF-1 production, but it also aids in the movement of cells showing aberrant CXCR4 expression into the bloodstream. Cells overexpressing CXCR4 extravasate into the tumor microenvironment, which contains high levels of ligand SDF-1, and the homing of these cells leads to cancer cells' metastasis.

3. Clinical significance of CXCR4 in different cancers

The studies in vitro are invariably an important first step in the overall process of establishing the credibility of any potential diagnostic and/or prognostic biomarker. However, the clinical data from actual patient-derived samples provides the critical validation. In case of CXCR4 signaling, there is a wealth of clinical data supporting its role in pathogenesis of various human cancers. One of the most important phenomenon responsible for cancer-associated mortality is cancer metastasis. For example, the brain metastasis from primary breast cancers is associated with significantly reduced survival and there is evidence that ligand SDF-1 secreted by cancer-associated fibroblasts (CAFs) plays a role in attracting breast cancer cells to brain, resulting in brain metastases [34]. The important role of CXCR4-SDF-1 signaling in cancer progression and metastasis is increasingly being realized and in the following few sub-sections, we discuss the recent literature supporting a role of CXCR4 and/or SDF-1 as diagnostic/prognostic biomarkers and their role in cancer metastasis. The inclusion criteria for the studies discussed in this section is that they all have data from human patient-derived samples.

3.1. Diagnostic biomarker

A plethora of studies have evaluated CXCR4 and/or SDF-1 expression levels in cancer tissue(s) obtained from cancer patients which reported elevated levels; thus, supporting the possibility of exploiting CXCR4 signaling as a valid diagnostic biomarker (Table 1). In lung cancer, the number one cancer in terms of deaths in the United States [35] as well as globally [36], a possible use of CXCR4 as diagnostic biomarker has been suggested with the observation that CXCR4 is upregulated in lung cancer tissues [37]. Even in the relatively rare lung adeno-squamous carcinoma, CXCR4 is a possible diagnostic biomarker [38] with seventy out of seventy-eight patients expressing CXCR4 and forty-five out of seventy-eight patients expressing particularly higher levels of CXCR4. In esophageal cancer, CXCR4 gene expression was reported higher in 52 esophageal squamous cell carcinoma patients, compared to normal esophageal mucosae, in one study [39] and in 101 esophageal squamous cell carcinoma patients in another study [40]. In gastric cancer patient samples, CXCR4 was reported to be significantly increased, compared to distant and adjacent non-cancer tissues [41,42]. In head and neck adenoid cystic carcinoma, CXCR4 positivity was reported in 81% of patients suggesting its possible diagnostic importance [43]. In vulvar squamous cell carcinoma, while CXCR4 was virtually absent in pre-cancer tissues, a strong immunostaining was apparent in tumor tissues [44]. Also, CXCR4 is abundantly expressed in papillary thyroid cancer, compared to normal thyroids or nonmalignant tissues [45,46].

Pancreatic cancer is one of the highly aggressive human cancers and there seems to be data supporting a diagnostic role of CXCR4 in this cancer. In a meta-analysis that included eleven studies and an impressive 1439 pancreatic ductal adenocarcinoma patients, it was found that CXCR4 is significantly highly expressed in pancreatic tumors, relative to normal pancreatic tissues and that the CXCR4 associates with tumor progression with the levels significantly increased in higher grades pancreatic tumors [47]. In colorectal cancer, which happens to a be a relatively better studied one in terms of the evaluation of CXCR4 [48, 49], a study [50] found immunoreactivity of 89% of 186 colorectal adenocarcinoma patients for CXCR4. As an interesting observation in this study, CXCR4 was reported high in tumors < 5 cm than those ≥ 5 cm and in patients with tumor grade 1–2 than grade those with grade 3 tumors [50]. Another study reported elevated CXCR4 in all tumor tissues from 32 patients, relative to the levels in normal colon tissues [51]. Similarly, CXCR4 was significantly higher in 42 colorectal cancer samples, relative to 27 normal controls [52]. Thus, there seems to be data from multiple human cancers supporting a diagnostic importance of CXCR4 significance which can probably be exploited in clinics.

3.2. Metastasis

CXCR4 has also been linked to cancer metastasis [53]. In an evaluation of tumors from cervical cancer patients, CXCR4 was not only high in cancer patients, its levels were also higher in patients with lymph node metastases [54]. In lung cancer as well, CXCR4 is a risk factor for lymph node metastasis [55] with 84.8% patients with lymph node metastasis expressing CXCR4 in metastatic lymph nodes, which was higher than the expression of CXCR4 in non-metastatic lymph nodes. Similarly, CXCR4 and SDF-1 levels associated with TNM staging and cervical lymph node metastases of nasopharyngeal carcinoma [56]. CXCR4 has been associated with metastasis in colorectal cancer patients [52], pancreatic cancer patients [47], melanoma [57,58], lung

Table 1
Studies supporting diagnostic importance of CXCR4 signaling.

Cancer	Number of patients	Methodology	Observations	Study
Breast	40 Luminal B	IHC, Gene array	High CXCR4 in lymph nodes	Raschioni 2018 [62]
	–	IHC	High SDF-1 in lymph nodes	Gadalla 2019 [63]
Cervical	48	IHC	Higher CXCR4 in patients with lymph node metastasis	Dai 2017 [54]
Colorectal	186	IHC	89% of patients exhibit CXCR4 expression	Saka 2017 [50]
	32	qRT-PCR	Higher CXCR4 in cancer tissues	Yoshuantari 2018 [51]
	49			Mitchell 2019 [52]
Esophageal Squamous Cell Carcinoma	52	qRT-PCR	Higher CXCR4 mRNA in patient samples	Goto 2017 [39]
	101			Yang 2020 [40]
Gastric	120	IHC	High CXCR4 in cancer tissues and metastases	Yu 2018 [41]
	589	IHC	Higher CXCR4 in cancer tissues	Chen 2021 [42]
Lung	185	IHC	Elevated CXCR4 levels in lung adenocarcinoma tissues	Cong 2017 [37]
	110	qRT-PCR	CXCR4 is high in metastatic lymph nodes	Bi 2017 [55]
	78 (Adeno-squamous carcinoma)	IHC	89.7% patients positive for CXCR4 with 57.7% exhibiting high levels	Zhu 2020 [38]
Melanoma	35	IHC	High CXCR4 in patients with metastasis	Ipenburg 2019 [57]
	656	Meta-analysis	CXCR4 associates with lymph node metastasis	Alimohammadi 2021 [58]
Nasopharyngeal	102	qRT-PCR, western blot	Higher expression of CXCR4 and SDF-1 in cancer tissues	Li 2017 [56]
Oral	51	IHC	Higher CXCR4 and CD133 in lymph node metastasis	Gokulan 2021 [60]
Osteosarcoma	50	IHC	CXCR4 and CD133 associate with lung metastases	Mardani 2020 [59]
Pancreatic	1439	Meta-analysis	Higher CXCR4 in tumor tissues and metastases	Ding 2019 [47]
Thyroid Cancer	54 (Follicular)	IHC	CXCR4 determines tumor size and distant metastases	Werner 2018 [61]
	74 (Papillary)	IHC	CXCR4 is high in patient samples	Sirakriengkrai 2021 [45]
	115 (Papillary)	IHC	CXCR4 is high in patients	Cao 2021 [46]
Vulvar	46	IHC	CXCR4 high in tumor samples	Rusetska 2021 [44]

adenosquamous carcinoma [38] and papillary thyroid cancer [46]. In osteosarcoma, a correlation of CXCR4 with lung metastasis was found, but only in association with the other stem cell marker CD133 [59] and, interestingly, a similar correlation between CXCR4 and CD133 but in lymph node metastases from primary oral squamous cell carcinoma has also been reported [60]. Elevated levels of CXCR4 have also been associated with TNM staging, lymph node metastases as well as distant metastases in gastric cancer [41] and follicular thyroid cancer [61]. In samples from patients with luminal B breast cancer, CXCR4 levels are high in lymph nodes suggesting a role of CXCR4 in lymph node metastasis [62]. Another study reported significantly high immunostaining of SDF-1 in patients with positive lymph nodes, compared to those with negative lymph nodes [63]. In summary, CXCR4 expression seems to correlate with metastasis, particularly lymph node metastasis in many different cancers.

3.3. Prognostic biomarker

In addition to the possible diagnostic importance of CXCR4 signaling, there has been emergence of consistent data supporting a possible prognostic importance of CXCR4 and SDF-1 (Table 2). In esophageal cancer, higher CXCR4 expression in the cytoplasm and nuclei correlated with poor cause-specific survival [39] while the patients with high levels of ligand SDF-1 tended to have worse overall survival and disease-free survival [64]. In follicular thyroid cancer, CXCR4 expression has been reported to associate with poor overall and recurrence-free survival [61]. A meta-analysis reported an association of CXCR4 with poor survival in patients with pancreatic ductal adenocarcinoma [47]. In osteosarcoma patients, an effect of CXCR4 on metastasis-free survival was reported, with a 72 months metastasis-free survival in patients without CXCR4, compared to just 14 months metastasis-free survival in patients positive for CXCR4 [65]. Similar association of CXCR4 with poor overall survival in esophageal squamous cell carcinoma [40], gastric cancer [42] and oral squamous cell carcinoma [60] has also been reported.

In a colorectal cancer study with 60 patients, the patients with CXCR4 expression had a worse 5-year survival, compared to CXCR4-negative patients [66]. This was further confirmed in a meta-analysis wherein receptor CXCR4 and its ligand SDF-1 were found to predict reduced disease-free survival and overall survival [67]. Other studies have also suggested a prognostic importance of CXCR4 or SDF-1 in colorectal cancer patients [52,68,69]. Further, a role of CXCR4 polymorphism in colorectal cancer prognosis has also been suggested with a common variant, CXCR4 rs2228014 linked to poor progression-free survival [70]. Interestingly, a possible role of CXCR4 polymorphism in breast cancer prognosis has also been suggested [71].

In lung cancer, CXCR4, in combination with Notch1, correlated with nodal stage, tumor stage and lymphovascular invasion in addition to poor prognosis [37]. Also, high CXCR4 at primary lung site while high SDF-1 at metastatic lymph nodes are determinants of poor overall survival [72]. CXCR4 has prognostic importance in the rare lung adenosquamous carcinoma and correlates with decreased overall and disease-free survival [38]. In a head and neck squamous cell carcinoma study [73], while no association between CXCR4 or SDF-1 with metastasis free survival or overall survival could be established, SDF-1 was still found to be a negative prognostic biomarker for loco-regional control after postoperative radiochemotherapy. This, however, is different from the observations in a study comprising of head and neck adenoid cystic carcinoma patients wherein CXCR4 was reported as an independent prognosis biomarker for poor recurrence-free survival [43]. In nasopharyngeal carcinoma, however, patients with higher CXCR4 and SDF-1 had significantly reduced survival, compared to those with lower expression [56]. Taken together, all this evidence supports a negative correlation between CXCR4/SDF-1 expression and good prognosis of cancer patients, and should be something that the attending clinicians might look out for, at the end of regular therapy.

4. Epigenetic regulation of CXCR4 signaling

Epigenetic regulation is the way a cell controls the expression of its genes, and this regulation defines how the cell functions. There are many machineries a cell can deploy to manipulate the expression of genes. Commonly, epigenetics could be manipulated using non-coding RNAs, such as microRNAs (miRNAs) [74,75], long non-coding RNAs (lncRNAs) [76,77] and circular RNAs (circRNAs) [78,79]. Other examples of common types of epigenetic gene expression regulation include

Table 2
Prognostic importance of CXCR4 signaling, as revealed in clinical studies.

Cancer	Number of patient samples (n)	Methodology	Observations	Study
Colorectal Cancer	60	IHC	CXCR4 expression correlates with poor 5-year survival	Ogawa 2017 [66]
		Meta-analysis	CXCR4-SDF-1 predict poor overall survival	Li 2017 [67]
	874	PCR sequencing	CXCR4 variant rs2228014 predicts progression-free survival	Matsusaka 2017 [70]
	49	qRT-PCR	CXCR4 determines overall survival	Mitchell 2019 [52]
	78	IHC	CXCR4 predicts response to chemotherapy	Ottaiano 2020 [68]
Esophageal Squamous Cell Carcinoma	172	IHC	High CXCR4 correlated with poor cause-specific survival	Goto 2017 [39]
	101		CXCR4 associates with poor overall survival	Yang 2020 [40]
	55	IHC	High SDF-1 patients have worse overall and disease free survival	Goto 2021 [64]
Head & Neck Cancer	201	IF	SDF-1 negatively correlates with loco-regional control	De-Colle 2017 [73]
	66	IHC	CXCR4 correlates with poor recurrence-free survival	Nulent 2020 [43]
Lung Cancer	185	IHC	Correlates with poor prognosis	Cong 2017 [37]
	140		CXCR4 and SDF-1 predict poor prognosis	Katsura 2018 [72]
	78		CXCR4 associates with decreased overall and disease-free survival	Zhu 2020 [38]
Nasopharyngeal Carcinoma	102	IHC	CXCR4 and SDF-1 correlate with shorter survival	Li 2017 [56]
Osteosarcoma	73	IHC	CXCR4 significantly reduces recurrence-free survival	Gong 2020 [65]
Pancreatic Cancer	1439	Meta-analysis	CXCR4 associates with poor survival	Ding 2019 [47]
Thyroid Cancer (Follicular)	72	IHC	CXCR4 correlates with poor overall and recurrence-free survival	Werner 2018 [61]

IHC: Immunohistochemistry

methylation (which is commonly associated with gene silencing) and acetylation (which is commonly associated with gene activation). A number of studies have been reported that support epigenetic regulation of CXCR4 by non-coding RNAs, methylation or acetylation. The sub-sections to follow discuss such aspects of CXCR4 regulation.

In addition to direct epigenetic regulation of CXCR4, as mentioned above, there are some indirect mechanisms by which the epigenetics of CXCR4 gene could be influenced. Transcription factors often influence gene expression, and for CXCR4, nuclear respiratory factor- 1 [1] and hypoxia-inducible factor 1-alpha [30] are responsible for the upregulation of the transcription of CXCR4. Furthermore, some growth factors are known to increase CXCR4, such as, hepatocyte growth factor [30]. Additionally, the extracellular conditions also have an ability to affect the expression of CXCR4, for example, hypoxia not only induces CXCR4 production in cancer tissues, but it also stabilizes CXCR4's expression [80]. However, some molecules, such as, acetyl-11-keto-β-boswellic acid reduce the expression of CXCR4 gene, which results in changes in the cancer behavior, including, reduced invasion and migration [81]. Hence, there are many ways, direct as well as indirect, through which the expression of CXCR4 can be epigenetically controlled.

4.1. *Effect of non-coding RNAs on CXCR4 expression*

4.1.1. *Effect of miRNAs on CXCR4*

miRNAs represent a major class of non-coding RNAs that play an essential part in regulating gene expression [82,83]. After being transcribed from the DNA, miRNAs typically bind to the 3' untranslated region of their target(s) mRNA(s) to tag them for degradation or to block translation [82]. However, in certain cases, miRNA can even upregulate certain genes [82,84]. Therefore, miRNA can epigenetic regulate the expression of genes in multiple ways.

The ability of miRNAs to control the expression of CXCR4 has been demonstrated in a range of different cancers. In many of these cases, miRNA inhibits the production of CXCR4. Examples of this include; miR-146 [85], miR-193-5p [86], miR-206 [87], and miR-622 [88] in colorectal cancer (CRC) cells; miR-622 in hepatocellular carcinoma [89]; miR-126 and miR-221 in lung cancer [90]; miR-139 in breast cancer [91]; miRNA-34a and miR-200c down regulate CXCR4 through targeting HIF1-a in breast cancer [92]; mir-155 indirectly reduces CXCR4 levels in glioblastoma [93], miR-126 in gastric cancer [94]; miR-381 in pancreatic ductal adenocarcinoma [95]; miR-143 inhibits CXCR4 expression in melanoma cancer cells by inhibiting proliferation and migration and facilitating apoptosis [96]; miR-143 inhibits the expression of CXCR4 in oral squamous cell cancer [97]; miR-330 decreases the expression of CXCR4 in melanoma [98]; miR-204 indirectly inhibits cxcr4 expression through the NF-κB signaling pathway in nasopharyngeal carcinoma [99]; miR-140-3p inhibits CXCR4 expression through targeting of its 3'UTR in colorectal cancer [100], and nasopharyngeal carcinoma [101]; miR-381-3p decreases the mRNA and protein expression of CXCR4 in non-small cell lung cancer cells [102]; miR-494-3p was proven to inhibit CXCR4 production post-transcriptionally in Synovial sarcoma, prostate and breast cancer cells [103]; miR-193a-5p negatively regulates the expression of CXCR4 mRNA in colon cancer cells, which decreases the migration and metastasis of these cells [104]; miR-133b down regulated the expression of CXCR4 in colon cancer cells SW-480 and SW-620, which inhibited invasion and migration and the proliferation of the cells [105]; miR-613 directly shuts off the expression of CXCR4 and has a tumor suppressor effect in inhibiting cancer phenotypes in osteosarcoma cells [106]; miR-302a was proven to decreased CXCR4 levels in breast cancer [107]; miR-128 was shown to reduce CXCR4 protein levels in human thyroid cancer cells [108]; miR-1246 directly inhibits CXCR4 expression, hence inhibiting the renal cell carcinoma cell's ability to proliferate and migrate [109], as well as it inhibits CXCR4 in lung cancer cells [110]; miR-9 is a tumor suppressor that works by inhibiting growth and metastasis of glioblastoma cells by inhibiting CXCR4 mRNA [111], and

evidence from acute myeloid leukemia has also proved that miR-9 is responsible for inhibiting invasion, migration, proliferation, and apoptosis resistance of these cells, through the inhibition of CXCR4 mRNA and protein expression [112]. Hence, multiple miRNAs play an important role in the epigenetic inhibition of CXCR4 expression in a variety of cancers.

In addition to the suppression of CXCR4, in a few cases, it has been recognized that miRNAs could have an up-regulatory effect on CXCR4. Examples of this include let-7 f in human mesenchymal stem cells that are associated with breast cancer [113]. The expression of CXCR4 was also positively regulated by miR-301a in osteosarcoma [114]. Not only does miR-410 upregulate CXCR4 in non-small cells lung cancer, but it also increases the stemness of these cells [80].

4.1.2. Effect of circRNAs on CXCR4

Circular RNAs are the relatively new class of non-coding RNAs that are attracting attention for their role in cancer pathogenesis [78,115, 116]. In last few years, some reports have emerged detailing a role of circRNAs in regulating CXCR4 signaling (Table 3). For example, in an early report on a possible connection between circRNAs and CXCR4 in cancer, it was shown that the oncogenic circ_0056618 is overexpressed in gastric cancer tissues and it sponges miR-206 reducing this miRNA's levels to attenuate the repression of CXCR4 [117]. Thus, elevated levels of circ_0056618 correlate with increased CXCR4 levels in gastric cancer. A similar role circ_0056618 has since been observed in colorectal cancer as well [87]. Here also, circ_0056618 sponged miR-206 and thus activated CXCR4. In addition to CXCR4, this study found similar effects of circ_0056618-miR-206 on VEGF-A, which could explain the positive regulation of angiogenesis by circ_0056618-miR-206 axis [87].

A bioinformatics-based study, that analyzed expression profiles of pancreatic ductal adenocarcinoma from multiple GEO databases, concluded that CXCR4 is one of the five hub genes overexpressed in pancreatic cancer [118]. Further, the analysis revealed that CXCR4 is regulated by circ-UBAP2 and hsa-miR-494 and that CXCR4 levels correlate with levels of M2 macrophages, a macrophage subtype with important role in tumor progression [119].

The circRNA-CXCR4 axis has been reported in several other cancers as well. circRNA ABCB10 has an up regulatory effect on the expression of CXCR4 in head and neck laryngeal squamous cell carcinoma [120]. Suppression of this circRNA reduced invasion and miR-588 was identified as the miRNA sponged by ABCB10 that could, in turn, target CXCR4. Circ_SLIT3 can sponge miR-223 leading to CXCR4 upregulation and increased tumor growth in hepatocellular carcinoma [121]. circFGFR1 is a circRNA that regulates the expression of CXCR4, through the sponging/inhibition of miR 381-3p in NSCLC cells [102]. This circRNA is upregulated in NSCLC tissues and correlates with poor prognosis of patients. circFGFR1 promotes glioma progression as well [122] by sponging miR-224 and upregulating CXCR4. In colorectal cancer, circN4BP2L2 is another circRNA that promotes cancer growth [123]. This circRNA sponges miR-340 and upregulates CXCR4 to induce tumor growth and metastasis.

A possible regulation of CXCR4 by circular RNAs with implications on cancer metastasis has been suggested in lung cancer. Similar to many studies detailed above in the section on diagnostic importance of CXCR4, this study also observed elevated CXCR4 levels in lung cancer patients with lymph node metastasis [124]. Further, circRNA_0056616 levels, as evaluated in released exosomes, were also high in patients with metastatic disease [124]. circRNAs can not just regulate CXCR4 but its ligand SDF-1 as well. In a study on melanoma, circ_0020710 was firstly found to be elevated in melanoma tissues, as determined by qRT-PCR, thus establishing its oncogenic role in melanoma [125]. Mechanism-wise, circ_0020710 upregulated SDF-1 through its sponging of miR-370-3p.

Table 3
CXCR4 signaling regulating circular RNAs.

Circular RNA	Cancer	miRNA	Pathological Effect	Reference
ABCB10	Head & Neck	miR-588	ABCB10 and CXCR4 promote tumor growth	[120]
circFGFR1	NSCLC	miR-381	circFGFR1 promotes tumor progression and immune evasion	[102]
	Glioma	miR-224	circFGFR1 supports glioma progression	[122]
circN4BP2L2	Colorectal	miR-340	Promotes tumor growth and metastasis	[123]
circ_SLIT3	Hepatocellular	miR-223	circ_SLIT3 promotes tumor growth	[121]
circ_0056616	Lung	*NE*	circRNA_0056616 and CXCR4 levels elevated in metastatic patients	[124]
circ_0056618	Gastric	miR-206	circ_0056618 highly expressed in tumor tissues and negatively correlates with survival	[117]
	Colorectal		circ_0056618 is elevated in tumor tissues and promotes angiogenesis	[87]
circ_0020710	Melanoma	miR-370-3p	circ_0020710 upregulates SDF-1 and promotes melanoma progression	[125]
circ-UBAP2	Pancreatic	miR-494	CXCR4 mediates immune responses within tumor microenvironment	[118]

NE: none evaluated

4.1.3. Effect of lncRNAs on CXCR4

LncRNAs' role in cancer metastasis and progression is increasingly being realized [77,126–129]. It is also being realized that lncRNAs exhibit regulatory effects on CXCR4 gene expression and CXCR4-SDF-1 signaling (Table 4). In an early report on the topic, lncRNA MALAT1 was investigated in human hilar cholangiocarcinoma and found to be expressed at higher levels in the samples obtained from cholangiocarcinoma patients [130]. This lncRNA MALAT1 associated positively with tumor stage and was reported to interact with miR-204 leading to increased growth, migration and invasion of cholangiocarcinoma cells through the upregulated CXCR4. miR-204 is also sponged by another lncRNA, LINC00922, which is upregulated in lung cancer cells [131]. Additionally, LINC00922 is associated with poor prognosis, as it enhances proliferation, and inhibits the CXCR4 expression suppressor miR-204 by competitively binding to it [131]. Lung cancer progression is further affected by lncRNA NORAD, which is elevated in NSCLC patients tissues as well as cell lines [132]. Inhibition of NORAD negatively affects cell growth because of reduced CXCR4 and SDF-1.

LncRNA HOTAIR, down regulates the expression of miR-126, thereby increasing CXCR4 expression in gastric cancer [94]. Another lncRNA, HNRNPKP2, also positively affects CXCR4 expression which possibly correlates with increased proliferation, migration invasion and even hepatic metastases of gastric cancer [133]. LncRNA COL1A1-014 is elevated in gastric cancer tissues as well as cell lines and its overexpression leads to elevated mRNA levels of ligand SDF-1 and elevated protein levels of both CXCR4 and SDF-1 [134]. lncRNA FER1L4, on the contrary, is a tumor suppressor lncRNA in gastric cancer cells whose overexpression reduces CXCR4 and SDF-1 resulting in reduced cell proliferation, invasion and lymphatic metastasis [135].

LncRNA GAS5 was shown to positively correlate with proliferation and invasion of esophageal cancer cells but through downregulation of CXCR4 [136]. Such activity of GAS5 was through its sponging of miR-301a. LncRNA UCA1 can also sponge miR-301a and thus affect CXCR4 expression, as shown in a study performed in osteosarcoma cells [114]. Additionally, UCA1 has been reported to sponge miR-204 in prostate cancer cells leading to increased growth and invasion through

Table 4
CXCR4 signaling regulating long non-coding RNAs.

LncRNA	Cancer	miRNA sponged	Pathological effect	Reference
COL1A1-014	Gastric	miR-1273h	Promotes cell growth	[134]
DLEU1	Pancreatic	miR-381	Upregulates CXCR4	[95]
DUXAP8	Thyroid	miR-223	Upregulates CXCR4	[143]
FER1L4	Gastric	*NE*	Downregulates CXCR4 and SDF-1	[135]
FEZF1-AS1	Osteosarcoma	miR-144	Promotes Warburg effect and proliferation	[138]
GAS5	Esophageal	miR-301a	Downregulates CXCR4	[136]
HILAR	Renal	miR-613	Induces cancer metastasis	[144]
HNRNPKP2	Gastric	*NE*	Induces cell proliferation, invasion and hepatic metastasis	[133]
HOTAIR	Gastric	miR-126	Upregulates CXCR4	[94]
LINC00922	Lung	miR-204	Upregulates CXCR4	[131]
LSINCT5	Ovarian	*NE*	Induces proliferation, migration and invasion through upregulated CXCR4	[139]
MALAT1	Cholangiocarcinoma	miR-204	Induces cell growth, migration and invasion through elevated CXCR4	[130]
	Leukemia	miR-146a	Sponges miR-146a to inhibit CXCR4	[141]
NEAT1	Retinoblastoma	miR-204	Correlates positively with CXCR4 in vitro and in vivo	[140]
NORAD	Lung	*NE*	Upregulates CXCR4 and SDF-1	[132]
TUG1	Tongue squamous	miR-133b	Determines resistance against cisplatin	[145]
UCA1	Osteosarcoma	miR-301a	Supports cell growth	[114]
	Prostate	miR-204	Induces cancer cell growth and metastasis	[137]
	Leukemia	*NE*	Upregulates CXCR4	[142]

NE: none evaluated

elevated CXCR4 [137]. In osteosarcoma cells, lncRNA FEZF1-AS1 sponges miR-144 and induces CXCR4 along with regulation of Warburg effect and suppression of apoptosis [138].

In ovarian cancer patients, lncRNA LSINCT5 was reported to be expressed at higher levels, relative to the normal ovarian tissue [139], especially in lymphatic metastases. Silencing of LSINCT5 reduced cell proliferation, migration and invasion through downregulation of CXCR4. lncRNA NEAT1 also correlated positively with CXCR4 expression in retinoblastoma tissues and cells [140]. NEAT1 sponged miR-204, a suppressor of CXCR4, thereby positively regulating CXCR4 expression in vitro as well as in vivo.

In pancreatic ductal adenocarcinoma, lncRNA DLEU1 has an oncogenic function, as it was shown to sponge miR-381, a CXCR4 targeting miRNA [95]. Hence, DLEU1 has an indirect role in the upregulation of CXCR4. In acute myeloid leukemia, MALAT1 inhibits CXCR4 expression through the sponging of miR-146a [141], while UCA1 induces CXCR4 expression [142]. In papillary thyroid cancer, DUXAP8 lncRNA upregulates CXCR4 through targeting of miR-223 [143] while in renal cancer, lncRNA HILAR promotes renal cancer metastasis through sponging of miR-613 and upregulation of Notch and CXCR4 signaling [144].

LncRNAs have also been found to regulate CXCR4 signaling with resulting effects on sensitivity to therapy. For example, in a study that recruited twenty-one cisplatin sensitive vs. resistant tongue squamous cell carcinoma patients [145], higher lncRNA TUG1 levels were found in the resistant patients. TUG1 targeted miR-133b and therefore overexpression of miR-133b suppressed cisplatin resistance. miR-133b, in turn, targeted CXCR4 which was elevated in resistant cells with increased TUG1. In summary, evidence for the regulation of CXCR4 by lncRNAs is slowly but surely emerging and in most of the reports lncRNAs-mediated regulation of CXCR4 involves sponging of specific miRNAs, a mechanism also seen in circRNAs-mediated CXCR4 regulation.

4.2. *Effect of methylation on CXCR4 expression*

An important epigenetic modification is the methylation of genes. Methylation takes place when a methyl group (CH_3) covalently binds to the 5'-carbon of a cytosine in the DNA, and this process is catalyzed by DNA methyltransferases (DNMTs) [146]. Targets of methylation in the genome that are associated with gene expression regulation are CpG islands, CpG shores, and first exons [146]. Methylation is typically viewed as a gene silencer as it prevents the DNA from interacting with transcription factors and chromatin proteins [147]. In cancer, DNA methylation or demethylation (removal of methyl groups) plays a large role in the activation or silencing of tumor related genes [148]. The state of methylation of specific cancer-related genes can be used as a tumor biomarker [146]. The methylation of cancer-related genes is specific and different across different cancers [146]. Hypermethylation is often observed in the promotor regions of tumor suppressor genes in cancer, and protection against methylation is observed in the promotors of oncogenes [146].

The gene expression of CXCR4 is highly affected by methylation [149]. In a breast cancer study, the CXCR4 gene was observed to be significantly hypomethylated, and this provides an epigenetic explanation to the overexpression of CXCR4 in these cells [149]. Compared to regular breast tissue (48%), the hypomethylation was abundant in cancerous breast tissue (78%), which makes methylation a possible marker for breast cancer. In another breast cancer study, it was seen that the methylation status of CXCR4 directly correlated with metastatic status of the tumors [150]. For example, metastasis to the lymph nodes was associated with the lack of CXCR4 promotor methylation. Furthermore, another study about breast cancer showed that in 67% of the breast cancer samples analyzed, there was a loss of methylation in the promotor region of CXCR4 gene, and this observation was associated with different phenotypes including tumor size, metastatic potential, tumor stage and patient survival [151]. Therefore, the methylation status of the CXCR4 gene influences breast cancer tumor progression.

In colorectal cancer, an increased expression of CXCR4 associated with high levels of 5-hydroxymethylcytosine (5hmC) in the CXCR4 gene [152]. Generally, 5hmC is an epigenetic marker that can represent an active demethylation intermediate. Therefore, in colorectal cancer, it is suggested that CXCR4 is overexpressed through its tagging for increased transcription by 5hmC. However, in pancreatic cancer cell lines, wherein the expression of CXCR4 was downregulated, hypermethylation was observed [153]. Whereas, these observations, on one hand document a role of methylation in regulation of CXCR4 expression in pancreatic cancer, but, on the other hand also suggest that not all pancreatic cancers might rely on the CXCR4 signaling pathway for the activation of cancer phenotypes and/or cancer progression. This also makes case for the argument that the use of CXCR4 inhibitors might not

prove an effective form of therapy against certain cancers or cancer subtypes. Additionally, a study about melanoma utilized a demethylating agent to investigate the effect of epigenetic modification on CXCR4 gene expression [154]. The inhibitor 5-Aza-2-deoxycytidine (5-Aza) was used for 4 melanoma cell lines. In three of four cell lines, 5-Aza had an inhibitory effect on CXCR4 gene expression, and, in one of the cell lines, where CXCR4 is typically hypermethylated, the demethylation using 5-Aza led to increase in the expression of CXCR4. Therefore, methylation plays a role in the expression of CXCR4 in melanoma.

4.3. Effect of histone acetylation on CXCR4 expression

Histone acetylation is another mechanism for the epigenetic regulation of genes. Histone acetylation involves the addition of an acetyl group on a ε-amino lysine residue in a histone [155]. This allows the chromatin structure to relax, and separates the DNA slightly from the histone, creating space for transcription regulators to access the DNA [156]. The effect that histone acetylation has on transcription is that of activation, and the process is carried out by acetyltransferases [157]. The enzyme histone deacetylase (HDAC) is responsible for removing acetyl groups, and HDAC inhibitors (such as n-butyrate) have been extensively used to study the effect of acetylation on cancer progression [158–160]. In cancer, the epigenetic regulation of cancer related genes (oncogenes or tumor suppressors) can affect the tumorigenesis or progression of the cancer [161]. Generally, there is a dysregulation of the histone acetylation of tumor suppressors and oncogenes in a way that favors tumor progression. Additionally, patient prognosis can be predicted using the loss of acetylation biomarkers. Hence, it is important to study histone acetylation in the activation of oncogenes and the suppression of tumor suppressors in human cancers, using appropriate models. The importance of acetylation in cancers is supported by the approval of four HDAC inhibitors, namely, vorinostat, romidepsin, panobinostat and belinostat by United States Food and Drug Administration (US-FDA) [162,163].

An important molecule in suppressing immunity and inducing skin cancer is platelet-activating factor (PAF) [164]. This mediator of inflammation in skin cancer upregulates the expression of CXCR4 through histone acetylation near the promotor region [164]. Hyperacetylation of the promotor region of CXCR4 is associated with migration in mast cells in skin cancer, making acetylation an important aspect of melanoma progression. In advanced prostate cancer, the transcription factor Ac-KLF5 is associated with the differentiation of osteoclasts and inducing metastatic bone lesions [165]. As a mechanism, Ac-KLF5 upregulates the expression of CXCR4 through histone acetylation of the promotor region of the CXCR4 gene [165]. Additionally, this study showed that upon the inhibition or knockdown of CXCR4 there was an abolition of advanced prostate cancer metastasis to bones and osteoclast differentiation. Hence, the effect of histone acetylation of the CXCR4 promotor is essential in metastasis of advanced prostate cancer.

In a breast cancer study, acetylation proved to indirectly manipulate the epigenetic expression of CXCR4 [156]. The HDAC inhibitor used was trichostatin A (TSA), and it worked by inhibiting the deacetylation on the promotor of the miRNA gene MIR146A of miR-146a, which promoted its upregulation. Since miR-146a has an inhibitory effect on the transcription and subsequent expression of CXCR4, an inhibitory effect on the production of CXCR4 was seen upon TSA addition. Breast cancer cells have a lower expression of miR-146a, and this relates to poor prognosis of patients. However, it could be inferred that with reversal of this effect i.e. upregulation of miR-146a through acetylation, the prognosis could be a improved. Thus, histone acetylation affects the expression of CXCR4 which subsequently positively impacts breast cancer progression and prognosis.

In chronic lymphocytic leukemia, HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) was used to study the expression of CXCR4 [166]. This study revealed that upon exposure of cells to SAHA, the gene expression level of CXCR4 was decreased, which reduced the migration of the leukemia cells. Even though the exact mechanism for the blocking of CXCR4 expression by HDACi is not fully established, accumulating data indicates that HDAC inhibitor TSA reduces CXCR4 expression and might thus be a candidate for cancer therapy.

5. Conclusions and future perspectives

Based on the studies discussed in this article, it is apparent that CXCR4 signaling plays a critical role in the pathogenesis of various human malignancies and is involved in proliferation, invasion, angiogenesis and metastasis of tumors (Fig. 1). This is the collective conclusion from a plethora of studies that include in vitro, in vivo as well as clinical studies/trials. Additionally, a case has been made for possible diagnostic as well as prognostic importance of CXCR4 signaling. This calls for design of further studies to cement the clinical importance of CXCR4 signaling in order to help shape future therapeutic strategies for the benefit of cancer patients. To certain extent, initial evaluations for feasibility are already in progress. For example, in a breast cancer study, the diagnostic performance of CXCR4-directed PET imaging has been evaluated in patients given the encouraging data from both clinical and pre-clinical studies. This evaluation revealed that CXCR4-targeted PET imaging does not confer advantage as a general diagnostic tool for breast cancer imaging, particularly when compared with established techniques for tumors detection [167]. The study was a relatively small one with limited number of patients. Additionally, there needs to be a word of caution because CXCR4 targeting might be beneficial for only a subset within a patient population, or a cancer subtype. For instance, again in breast cancer, it was reported that inhibition of CXCR4 signaling, through the use of specific inhibitors AMD3100 and TN14003, could suppress tumor growth and metastasis in both therapy-sensitive and therapy-resistant HER2-overexpressing breast cancers represented by patient-derived xenografts [168]. This is an encouraging news supporting the logic behind targeting CXCR4 even in therapy-refractory cancers. However, the same study also noted that inhibition of CXCR4 in another subset of breast cancer, namely, triple negative breast cancer, could actually be counter-productive and may result in increased metastatic spread [168]. On a positive note, in a phase IIa study, antagonizing CXCR4 through the use of BL-8040/ motixafortide expanded the benefit of chemotherapy in pancreatic ductal adenocarcinoma patients, especially when combined with inhibitor of programmed cell death-1 (PD-1) [169]. All these observations suggest that identifying the right patient cohort/ cancer subtype as well as the combination treatments might be the strategy moving forward. The notion is further supported by a prognostic role of CXCR4 in response to chemotherapy [68] and the observation that SDF-1 is high in platinum-treated NSCLC patients with progressive disease and worse clinical prognosis [170].

Additionally, the epigenetic regulation of CXCR4 is evident at many levels with non-coding RNAs and methylation/acetylation, as discussed in this article, playing an important role in the eventual expression of CXCR4. It would therefore be interesting for the future studies to elucidate if HDAC inhibitors (such as the US-FDA approved HDAC inhibitors vorinostat, romidepsin, panobinostat and belinostat) can directly or indirectly affect receptor CXCR4 and/or ligand SDF-1 expression. Further, the post-translational modifications of CXCR4 such as phosphorylation, ubiquitination, glycosylation and sulfation can also potentially affect receptor-ligand interactions, and a better understanding of these can lead to novel strategies to regulate CXCR4 signaling. Moving forward, a more patient-centric and precision medicine-based approach combined with placebo-controlled, large scale clinical trials might be the best way to further evaluate and exploit the clinical value of CXCR4 signaling in cancer patients, and as a tool for imaging and targeted therapy.

CRediT authorship contribution statement

AA: Conceptualization, Supervision. **RKA, AQK, FA, AWA and AA**:

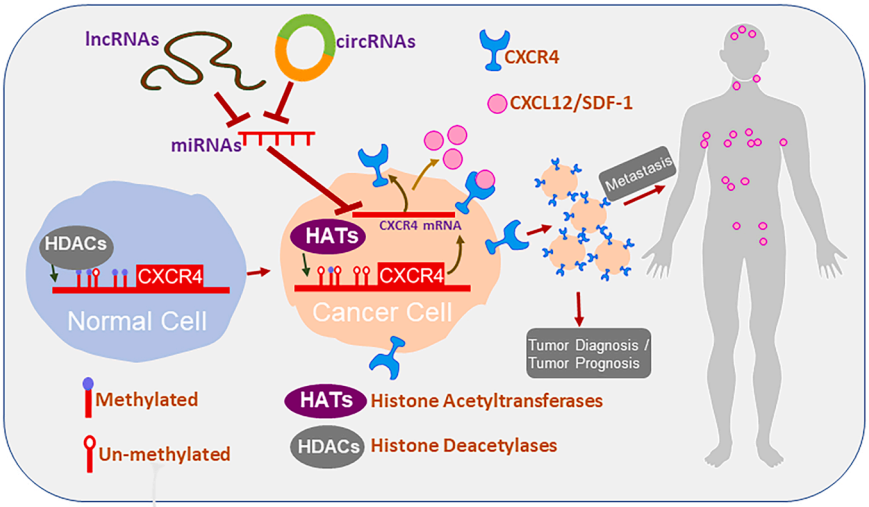

Fig. 1. CXCR4 in cancer progression. Expression of receptor CXCR4 can be induced by hypomethylation or acetylation leading to its recruitment at cell membrane. Additionally, non-coding RNAs, such as, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) can affect CXCR4 transcription regulation. Ligand CXCL12/SDF-1 can bind to CXCR4 thereby activating the signaling resulting in increased proliferation, invasion, angiogenesis etc. Increased SDF-1 release at various distant organs can attract cancer cells (with CXCR4 expression), resulting in homing of cancer cells at distant sites. Elevated CXCR4/SDF-1 levels have been proposed as promising diagnostic and/or prognostic biomarkers.

Writing – original draft. **MAA, JB, MS, SU and AA**: Writing – review & editing.

Acknowledgment

Open Access funding for this article has been provided by the Qatar National Library.

Conflict of Interest Statement

None of the authors have any conflict of interest to report.

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