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The CXCL8-CXCR1/2 pathways in cancer

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Abstract

Persistent infection or chronic inflammation contributes significantly to tumourigenesis and tumour progression. C-X-C motif ligand 8 (CXCL8) is a chemokine that acts as an important multifunctional cytokine to modulate tumour proliferation, invasion and migration in an autocrine or paracrine manner. Studies have suggested that CXCL8 and its cognate receptors, C-X-C chemokine receptor 1 (CXCR1) and CX-C chemokine receptor 2 (CXCR2), mediate the initiation and development of various cancers including breast cancer, prostate cancer, lung cancer, colorectal carcinoma and melanoma. CXCL8 also integrates with multiple intracellular signalling pathways to produce coordinated effects. Neovascularisation, which provides a basis for fostering tumour growth and metastasis, is now recognised as a critical function of CXCL8 in the tumour microenvironment. In this review, we summarize the biological functions and ficlinical significance of the CXCL8 signalling axis in cancer. We also propose that CXCL8 may be a potential therapeutic target for cancer treatment

Keywords

CXCL8; CXCR1; CXCR2; Cancer; Angiogenesis; Metastasis

1. Introduction

Long-lasting chronic infection is a hallmark of tumourigenesis. Inflammation caused by chemical and physical agents increases the risk of malignancy [1]. Inflammatory responses

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to numerous cytokines in the tumour microenvironment play a more crucial role in facilitating tumour growth, progression, and immunosuppression compared to rendering a potent anti-tumour effect [2].

CXCL8 which is recognised as a prototypical chemokine belonging to the CXC family is responsible for the recruitment and activation of neutrophils and granulocytes to the site of inflammation [3]. CXCL8 is almost undetectable in physiological states, but is rapidly induced by pro-inflammatory cytokines such as tumour necrosis factor a (TNFa) and interleukin-1b (IL-1b) [4]. The function of CXCL8 mainly relies on its interaction with specific cell surface G protein-coupled receptors (GPCR), CXCR1 and CXCR2 [5]. Ligation of CXCL8 with different receptors triggers signalling with distinct biological outcomes, even though CXCR2 is its primary functional receptor [5]. While CXCL8/CXCR1 mainly increases the proliferation of tumour cells, CXCL8/CXCR2 promotes angiogenesis in prostate cancer [6].

The mechanism of CXCL8-CXCR1/2 signalling in tumourigenesis and tumour progression has been explored extensively. CXCL8 is typically known to promote angiogenesis, but it also activates matrix metalloproteinase (MMP) that is involved in metastasisrelated tissue remodelling [7–9]. The CXCL8 signalling nexus directly influences the sensitivity of tumour cells to chemotherapies by altering pathways associated with apoptosis and multidrug resistance [10,11]. High levels of CXCL8 are indicative of an increased risk of cancer and poor disease prognosis [12,13].

In this review, we summarize our current understanding of CXCL8-CXCR1/2 signalling pathways and their role in initiation, immunosuppression, angiogenesis and metastasis of tumours. We discuss the implication of CXCL8 and its receptors as potential biomarkers for cancer diagnosis and prognosis as well as cancer therapeutic targets.

2. Structure of CXCL8 and CXCR1/2

CXCL8, also known as Interleukin-8 (IL-8), belongs to the elastin-like recombinamer (ELR) $^{+}$ CXC chemokines family. It is produced by macrophages, epithelial cells, airway smooth muscle cells and endothelial cells [14]. CXCL8 is initially produced as a protein of 99 amino acids that undergoes cleavage to form active CXCL8 isoforms, a 77 amino acid peptide in non-immune cells or a 72 amino acid peptide in monocytes and macrophages [5]. The gene encoding CXCL8 is located on chromosome 4q13-q21 [15]. Dimerisation of CXCL8 forms the structural basis for receptor binding [16].

CXCR1 and CXCR2, known as Interleukin-8 receptor A (IL-8RA) and Interleukin-8 receptor B (IL-8RB), respectively, are members of the GPCR family which contains 7 transmembrane domains (Fig. 1A–D) [17]. IL-8RA, IL-8RB and IL8RBP (a pseudogene of IL8RB) form a gene cluster in a region located on chromosome 2q33-q36 [18]. CXCR1 interacts with CXCL6 and CXCL8, whereas CXCR2 binds to CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7 and CXCL8 with high affinity [19]. Both CXCR1 and CXCR2 are expressed on granulocytes, monocytes, mast cells and some natural killer cells [20]. CXCR1 interacts with CXCL8 through its N-terminal b strand [16]. The simulated tertiary

structures of the interaction model between CXCL8-dimer and CXCR1 N-terminal are shown in Fig. 1E and 1F.

3. Intracellular signalling pathways of CXCL8

3.1. Activation of phospatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK)

PI3K acts as the major downstream intracellular signal of CXCL8 inducing phosphorylation of its substrate, Akt, which plays a critical role in modulating cell survival, angiogenesis, and migration [21,22]. CXCL8 also increases the expression of Akt in androgen-independent prostate cancer (AIPC) cell lines [3]. LY294002, GDC-0941 and BEZ235 are known potent inhibitors of PI3K.

MAPK signalling cascade consists of multiple serine/threonine kinases among which the best characterised is the Raf-1/MAP/Erk cascade. CXCL8 activates this classic signalling cascade in both neutrophils and cancer cells [23–26]. MAPK-targeted inhibitors such as vemurafenib, sorafenib, dabrafenib, trametinib, PD184352, SCH772984, and XMD8–92 may potentially interrupt the MAPK-associated signal transduction in tumours. Activation of p38 MAPK cascade downstream of CXCL8 has also been reported; however, its functional significance is yet to be determined [27]. CXCL8 activates MAPK signalling via PI3K in neutrophils [26], and via transactivation of epidermal growth factor receptor (EGFR) resulting in Ras-GTPase activation in ovarian and lung cancer cell lines [24,25]. A subsequent study suggests that PI3K is essential for CXCL8-induced migration of human neutrophils independent of MAPK signalling [21].

3.2. Activation of phospholipase C (PLC)

CXCL8 stimulates PLC signalling which in turn induces the phosphorylation of protein kinase C (PKC). CXCL8 promotes migration of human cancer cells by activation of the PLC-dependent PKC signalling pathway which when coupled with an increase in Ca^{2+} concentration regulates the actin cytoskeleton[28]. CXCL8 also regulates cyclin D1 expression in AIPC cells by activation of an atypical isoform of PKC, PKCj [23]. Enzastaurin, sotrastaurin, Go 6983, staurosporine and quercetin have been established as highly effective inhibitors of PKC *in vivo*.

3.3. Activation of non-receptor tyrosine kinases and Rho-GTPases

Non-receptor tyrosine kinases including Src family members and focal adhesion kinase (FAK) are involved in CXCL8-induced signalling cascades. CXCL8 signalling is positively correlated with an increase in phosphorylation of Src-kinases and FAK in cancer cells, which contributes to cell proliferation, cell survival, and chemoresistance [29,30]. A putative pathway linking PI3K signalling to the activation of FAK-Src has been described [3].

CXCL8 promotes motility and invasion of cancer cells via Rho-GTPases-induced polymerisation of actin cytoskeleton [3]. While CXCR1 rapidly stimulates Rho-GTPase in endothelial cells, activation of CXCR2 induces a delayed effect [31]. Moreover, Rho-

GTPase may promote phosphorylation of Src and FAK with further impact on downstream transcriptional factors [3].

4. CXCL8-CXCR1/2 axis in tumour immunosuppression

4.1. CXCL8 and myeloid-derived suppressor cells (MDSCs)

The functional importance of MDSCs in the immune response to tumours has been well described. MDSCs are identified as a highly heterogeneous population with myeloid progenitor cells and immature myeloid cells as two major components [32]. Based on their surface markers, MDSCs exhibit two distinct phenotypes and are defined as granulocytic MDSCs (GrMDSCs) and monocytic MDSCs (MoMDSCs) [33]. In 1995, human MDSCs were first proposed to infiltrate tumours and metastatic lymph nodes in head and neck cancer patients [34]. MDSCs suppress anti-tumour immune response mainly by inhibiting T cells via multiple molecular mechanisms [35–37].

In a recent investigation, CXCR1/2 were detected on the surface of tumour-derived MDSCs. CXCL8 was identified as a potent chemotactic stimulus for recruitment of MDSCs to tumour foci in a dose-dependent manner in a tumour engraftment mouse model [38]. Similar results were obtained from CXCL8-containing super-natants of HT29 colon carcinoma cells as well as from CXCL8-containing sera of patients [38]. In this study, only MoMDSCs from peripheral blood of cancer patients exhibited a suppressive effect on T-cells [38]. Interestingly, CXCL8 was found to induce GrMDSCs to release DNA to form Neutrophil Extracellular Traps (NETs), which were involved in thrombus formation and metastasis in cancer patients [38–40]. Moreover, the CXCR1/2 blocking agent, Reparisxin, abolished the above effects of CXCL8 *in vivo* [38].

4.2. The relevant mechanisms of tumour-associated neutrophils (TANs) and Epithelial–Mesenchymal Transition (EMT) in CXCL8-induced immune resistance

TANs are associated with poor clinical outcome and heavy tumour burden in most solid malignancies [41–49]. TANs exhibit two phenotypes that play diverse roles in the immune response to tumour. N1 TANs exert anti-tumour activity mainly via antibody-dependent cellular cytotoxicity and oxidative damage [50,51], as well as via enhancing immune surveillance by secreting multiple inflammation-associated cytokines [52]. In contrast, N2 TANs contribute to tumour neovascularisation and distant metastasis [53,54]. Arginase 1 secreted by N2 TANs was found to favour immunosuppression by restraining T-cell receptor expression, attenuating antigen-specific T-cell responses and recruiting T regulatory cells [35,55,56]. CXCL8 has been shown to chemoattract TANs to the tumour microenvironment in Ras-driven cancer [57–59]. It can be inferred that CXCL8-associated resistance to immune killing occurs mainly by attracting the N2 phenotype.

In addition to contributing to metastasis, EMT is proposed to confer tumour escape to immune destruction by inhibiting CTL lysis by inducing autophagy and reducing the formation of immunological synapse [60]. An autocrine feedback loop exists between CXCL8 and EMT. CXCL8 contributes to EMT and initiates the cytokines and/or growth

factors cascade including CXCL8 itself [61]. However, the mechanism of CXCL8-induced immunosuppression via EMT is still unknown.

5. The role of CXCL8-CXCR1/2 pathway in various cancer types

5.1. Breast cancer

CXCL8 can enhance the immunoregulatory ability to defend against cancer, and can also modify the microenvironment to facilitate tumourigenesis. In the context of breast cancer, the latter role is more dominant compared to the former. All breast cancer cells express CXCR1 and CXCR2 [62]. CXCL8 is also associated with growth receptors expressed on the surface of breast cancer cells. Increased CXCL8 has been mostly detected in oestrogen receptor (ER)-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor-2 (HER-2)/neu-positive breast cancers [62,63]. Moreover, CXCL8 increases the activity of breast cancer stem-like cells (CSCs) by transactivation of HER2 [64,65].

Breast cancer cell-derived CXCL8 cooperates with vascular endothelial growth factor (VEGF) to establish and expand tumour neovasculature [66]. Glucose deprivation and endoplasmic reticulum stress are regarded as effective upregulating factors of VEGF and CXCL8 [67]. Downregulation of CXCL8 significantly reduces the microvessel density (MVD) in ER-negative breast tumours *in vivo*, while it does not affect proliferation and cell cycle of cancer cells[68]. Paradoxically, anti-CXCL8 therapy alone is ineffective *in vitro* owing to the other compensatory angiogenic factors in supernatant such as monocyte chemotactic protein-1 (MCP-1), growth-regulated protein (GRO), VEGF, and TGF-b1 [69,70].

Tumour neovascularisation not only contributes to the initiation and growth of breast cancer but also offers blood supply for distant metastasis. The ectopic expression of CXCL8 stimulated by IL-1b and TNF-a can enhance the metastatic potential of breast cancer, as high level of CXCL8 can promote angiogenesis and attract neutrophils to release enzymes involved in tissue remodelling and tumour establishment [71]. Atypical methylation of two deoxycytidylate-phosphate-deoxyguanylate (CpG) sites (−1241 and −1311) upstream of the CXCL8 promoter counterintuitively upregulate the expression of CXCL8 in high metastatic cell lines, MDA-231 and MDA-345 [72]. As bone is a common site for breast cancer metastasis, it was suggested that cyclooxygenase-2 (COX-2)-mediated production of CXCL8 in the ER-negative breast cancer cells might contribute to both human osteoclast formation and bone resorption [73]. A novel tumour suppressor, Dachshund 1 (DACH1), inhibits CXCL8-induced breast cancer cell migration and metastasis through binding to the AP-1 and NF-kB binding sites of CXCL8 promoter [74].

Considering the significance of CXCL8 in the initiation, progression, angiogenesis and metastasis of breast cancer, CXCL8 is defined as an unfavourable prognostic factor. Elevated serum level of CXCL8 is associated with an advanced clinical status, a severe tumour load, and earlier distant metastasis [75]. In lymph node-negative breast cancer, patients with higher CXCL8 levels (>102.27 pg/mg) suffer a poor prognosis including shorter survival time and distant metastasis [76]. With the development of genomic sequencing in recent years, the single nucleotide polymorphism (SNP) of CXCL8 and CXCR2 indicates the

individual difference among different ethnic populations. The CXCL8 (−251) A allele and/or the CXCR2 (+1208) T allele are correlated with the increased risk and poor prognosis of breast cancer in Tunisian population [77]. Inversely, CXCL8 (−251) T allele (TT/TA) is associated with an increased risk in Asian population, but a decreased risk in African population [78]. However, the functional analysis of these SNPs in breast cancer has not been well explored. Influence of CXCL8 (−251) allele on its expression requires more in-depth research.

5.2. Prostate cancer

Increased CXCL8 secretion by prostate cancer (PCa) cells is associated with malignant biological behaviours of cancer cells. CXCL8/CXCR2 promote castration-resistant growth and proliferation of AIPC cells by activating cyclin D1 expression in a PI3K/Akt/mTOR and MAPK pathways-dependent manner [6,23]. In addition to binding to its receptors, CXCL8 also upregulates the expression of CXCR7, which directly interacts with EGFR to induce prostate cancer cell growth [79]. While CXCL8 promotes prostate cancer progression by recruiting adipose stromal cells (ASCs) to tumours, such chemotaxis is blocked by CXCR1/2-antibodies [80]. Phosphatase and tensin homologue (PTEN), a tumour suppressor gene, is frequently mutated in metastatic PCa [81]. PTEN-deficient prostate tumours may promote hypoxia-inducible factor-1 (HIF-1) and NF-kB, which in turn can upregulate the expression of CXCL8 resulting in sustained tumour development and accelerated tumour progression [82,83]. DACH1 inhibits CXCL8-mediated proliferation and migration of prostate epithelial cells by binding to its promoter and suppressing CXCL8 transcription in a tissue specific DACH1-knockdown model [84].

Poor clinicopathological features including high Gleason score and advanced pathological stage of PCa are associated with an increased mRNA expression of CXCL8 [85]. A combination of serum CXCL8 levels and free/total PSA ratios may provide a substantial improvement in distinguishing benign prostatic hyperplasia (BPH) from PCa and predicting disease outcome [86].

5.3. Lung cancer

Elevated CXCL8 was detected in lung cancer, especially in non-small cell lung cancer (NSCLC) cell lines [87–89]. The mitogenic role of CXCL8 in lung cancer is mediated mainly through CXCR1 or via transactivation of EGFR [25]. The combined effect of VEGF and CXCL8 on intratumoural angiogenesis of lung cancer has been verified [90]. Autocrine CXCL8 and VEGF collaboratively mediate neovascularisation and EMT, which facilitates invasion in A549 cells [91]. CXCL8 also mediates osteoclastogenesis in lung cancer patients via PLD/PKC/Erk1/2 or PLD/Akt signalling [92,93].

Early diagnosis is critical for lung cancer. Circulating CXCL8 may predict the risk of lung cancer, since it is upregulated prior to clinical diagnosis [12,94]. The National Cancer Institute-Maryland (NCI-MD) case–control study and the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial showed that high expression of CXCL8 can raise the risk of lung cancer by 45%−86% [12,94]. High CXCL8 mRNA levels were strongly associated with advanced stages, distant lymph node metastasis, shortened survival time and

early relapse of NSCLC [95,96]. As for SCLC, no statistical relevance was found between serum levels of CXCL8 and disease stage and tumour burden [97]. In conclusion, serum protein or tumour mRNA levels of CXCL8 can be an effective marker to monitor tumour occurrence and relapse in lung cancer patients.

5.4. Melanoma

CXCL8 is a predominant regulator of growth, angiogenesis and metastasis of melanoma in preclinical animal models [98–100]. The metastatic potential of CXCL8 relies on its ability to promote vascularisation, activate MMP-2, and enhance anoikis resistance [99,101]. Consistently, CXCL8 produced by melanoma cells correlates with tumour burden and poor prognosis [102]. However, controversies exist about whether both the receptors of CXCL8 impact melanoma progression. While CXCR1 alone is associated with CXCL8-mediated chemotaxis [103], CXCR2 upregulates CXCL8-mediated angiogenesis, invasion and migration of human melanoma cells independent of CXCR1 [104,105].

Anti-VEGF drug, bevacizumab, slightly increases CXCR2 expression in human umbilical vein endothelial cells and activates CXCL8 signalling as an alternative pro-angiogenic pathway in uveal melanoma [106]. Knockdown of host CXCR2 decreases growth, angiogenesis, and experimental lung metastasis [111]. Together, these studies indicate that inhibition of the CXCL8/CXCR2 axis with neutralizing antibodies may control melanoma neoangiogenesis and enhance the sensitivity to therapy.

5.5. Other cancers

Apart from the cancer types discussed above, CXCL8 signalling axis also plays an indispensable role in colorectal carcinoma [107,108], renal cell carcinoma [109], pancreatic cancer [110], thyroid tumours [111,112], gastric cancer [113–115], ovarian cancer [116], lymphomas [117], and haematologic malignancies [118–120]. As one of the markedly upregulated chemokines in colorectal carcinoma (CRC), CXCL8 has been demonstrated to induce CRC cell proliferation in an autocrine manner and enhance the resistance to anoikis [107,108]. Aberrant expression of CXCL8 is correlated with progression, VEGF-independent angiogenesis and chemoresistance of CRC *in vitro* and *in vivo* [121,122]. Demethylation of CXCL8 promoter region significantly increases its serum level, which correlates with distant metastasis, advanced Dukes stage and poor overall survival [123,124]. Notably, CXCL8 secreted by renal cancer cells induces the migration of mesenchymal stem cells (MSCs), which play a vital role in the development, metastasis, and drug resistance of cancers [125]. In clear cell renal cell cancer (ccRCC), resistance to kinase inhibitors such as sunitinib is accompanied with increased expression of tumour-derived CXCL8 [126]. Anti-CXCL8 could sensitize tumours to sunitinib treatment in a nude mouse model [126].

6. Targeted therapy research

6.1. Preclinical studies

Owing to the significant association between the CXCL8-CXCR1/2axis and certain types of tumours, targeted therapies against this axis are expected to have high clinical value in tumour treatment. Reparixin, a clinical grade CXCR1/2 inhibitor, was shown to block the

binding of CXCL8 to CXCR1/2 in a non-competitive manner and inhibit CXCL8-induced T lymphocyte and NK cell chemotaxis and migration in previous study [127]. Reparixin or CXCR1-antibody can selectively deplete CSCs and tumour cells via FASL/FAS signalling *in vitro* and can inhibit tumour growth and metastasis in a tumour xenograft model *in vivo* [128]. While reparixin and paclitaxel exhibited a synergistic effect towards arresting cell cycle and inhibiting tumoursphere formation *in vitro*, they showed an additive effect towards reducing brain metastasis *in vivo* [129]. In addition to reparixin, other small-molecule antagonists of CXCR1/2 such as SCH479833 and SCH527123 exerted anti-tumour activity in xenograft models of breast cancer [128], colorectal cancer [130], melanoma [131] and spontaneous colon cancer liver metastasis [132]. SCH563705 has been demonstrated to robustly inhibit primary human breast CSC activity [133]. In preclinical colon cancer models, the combination of SCH527123 and oxaliplatin was more potent in controlling cell proliferation and angiogenesis and inducing apoptosis compared to single agents [130]. G31P, another CXCR1/2 inhibitor, significantly reduced the viability, adhesion and migration of PC-3 cells *in vitro*, and inhibited the growth of transplanted PCa xenografts in a nude mouse model [134].

CXCL8 neutralising antibodies, ABX-CXCL8 and HuMax-CXCL8, are mostly used to block CXCL8-CXCR1/2 pathway in preclinical studies. ABX-CXCL8 had no effect on proliferation of bladder cancer cells *in vitro* but significantly inhibited tumour growth in a mouse model [135]. ABX-CXCL8-treated mice exhibited a significant reduction in tumour growth, angiogenesis and metastasis of human melanoma cells [136]. Mechanistically, ABX-CXCL8 suppresses tumour metastasis by downregulation of MMP-2 and MMP-9 *in vitro* [135].

6.2. Clinical trials

Based on the preclinical studies, reparixin is a potential candidate for clinical trial in breast cancer. An open label phase I clinical trial including 33 female patients diagnosed with HER-2-negative metastatic breast cancer was conducted to determine the pharmacokinetic profile and evaluate safety and tolerability of orally administered reparixin in combination with a fixed dose of weekly paclitaxel (NCT02001974). Subsequently, a double-blind phase II study with 190 estimated enrolments is in progress to compare the progression free survival of metastatic TNBC patients receiving paclitaxel alone or with reparixin (NCT02370238). Reparixin has also been introduced to prevent graft dysfunction after islet transplantation (NCT01220856), kidney transplantation (NCT00248040) and lung transplantation (NCT00224406) in phase II clinical trials. A phase Ib pilot study to perform gradient trial with HuMax-CXCL8 is recruiting patients with metastatic or unresectable, locally advanced malignant solid tumours (NCT02536469).

7. Conclusions

To date, great endeavours have been made to identify the roles of the CXCL8-CXCR1/2 pathways in human cancers. CXCL8 exerts multiple effects on biological activities of tumour cells including proliferation, invasion and migration, all of which are essential for tumour growth and metastasis. PI3K, Akt and Erk signalling pathways have been identified

to be involved in CXCL8-associated intracellular signals. A simplified signalling diagram is shown in Fig. 2 and detailed information is presented in Table 1. Interruption of the related signalling pathways may thus provide promising therapeutic avenues for tumours with high activity of CXCL8-CXCR1/2.

Given that high expression of CXCL8 and its receptors is associated with tumourigenesis and progression of certain types of tumours, these factors may serve as biomarkers in screening patients and evaluating prognosis. The CXCL8–CXCR1/2 pathways play a confirmed role in resistance to chemotherapy in breast cancer, prostate cancer and colorectal carcinoma. CXCL8-upregulated expressions of anti-apoptotic protein and thymidylate synthase (TS) may attenuate the efficacy of chemotherapies. Therefore, targeted-inhibition of CXCL8 may be an attractive therapeutic strategy to sensitise tumour cells to chemotherapeutic agents and eventually increase the survival of patients with end-stage disease. CXCL8 or CXCR1/2 may offer effective approaches for the development of targeted molecular therapeutics for tumours. Nevertheless, substantial investigations are warranted before practically applying the predictive, prognostic, and therapeutic value of CXCL8 signalling in human cancers.

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Abbreviations:

CXCL8	C-X-C motif ligand 8
CXCR1	C-X-C chemokine receptor 1
CXCR2	C-X-C chemokine receptor 2
TNFα	tumour necrosis factor α
IL-1β	Interleukin-1β
GPCR	G protein-coupled receptors
MMP	matrix metalloproteinase
IL-8	Interleukin-8
ELR	elastin-like recombinamer
IL-8RA	Interleukin-8 receptors A

IL-8RB	Interleukin-8 receptors B
PI3K	phospatidylinositol-3-kinase
MAPK	mitogen-activated protein kinase
AIPC	androgen-independent prostate cancer
EGFR	epidermal growth factor receptor
PLC	phospholipase C
PKC	protein kinase C
FAK	focal adhesion kinase
MDSCs	myeloid-derived suppressor cells
GrMDSCs	granulocytic MDSCs
MoMDSCs	monocytic MDSCs
NETs	Neutrophil Extracellular Traps
TAN	tumour-associated neutrophils
EMT	epithelial–mesenchymal transition
CSCs	cancer stem-like cells
HER2	human epidermal growth factor receptor 2
ER	oestrogen receptor
PR	progesterone receptor
SNP	single nucleotide polymorphism
VEGF	vascular endothelial growth factor
NF-κB	nuclear factor kappa B
MVD	microvessel density
MCP-1	monocyte chemotactic protein-1
GRO	growth-regulated protein
CpG	deoxycytidylate-phosphate-deoxyguanylate
COX-2	cyclooxygenase-2
TNFβ	tumour necrosis factor β
DACH1	Dachshund 1
TNBC	triple negative breast cancers

MDR	multidrug resistance
PCa	prostate cancer
PTEN	phosphatase and tensin homolog
NE	neuroendocrine
PSA	prostate-speci c antigen
BPH	benign prostatic hyperplasia
1α, 25-(OH)2 D3	1α, 25-dihydroxyvitamin D3
NSCLC	non-small cell lung cancer
SCLC	small cell lung cancer
ADC	lung adenocarcinoma
DFS	disease-free survival
OS	overall survival
NCI-MD	National Cancer Institute-Maryland
PLCO	Prostate, Lung, Colorectal, and Ovarian
CRC	colorectal carcinoma
ccRCC	clear cell renal cell cancer

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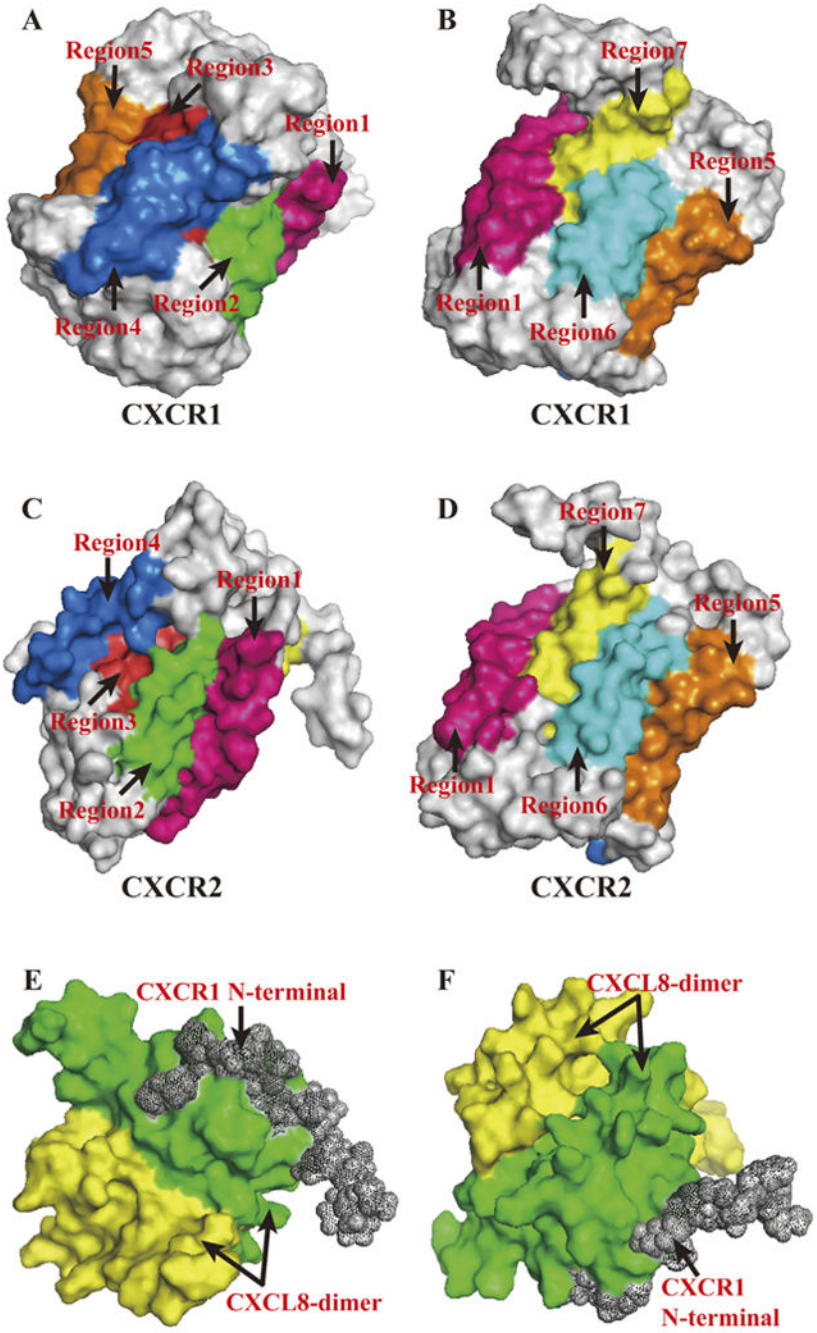

Fig. 1.

PyMOL Molecular Graphics System was used to present above structures. (A, B). Corresponding transmembrane regions within CXCR1 tertiary structure. Regions marked in different colours with arrows showed its seven transmembrane domains. Simulation of tertiary structure was constructed using PDB lefiof 2LNL produced by Park et al. [17]. (C, D). Corresponding transmembrane regions within CXCR2 tertiary structure. Regions marked in different colours with arrows showed its seven transmembrane domains. The amino acid sequence of CXCR2, NCBI RefSeq NP_0015481, were used to model CXCR2

tertiary structure in Swiss Model [155]. (E, F). Interaction model between CXCL8-dimer and CXCR1 N-terminal. Simulation of tertiary structure was constructed using PDB le of 1ILP produced by Skeltonfiet al. [16].

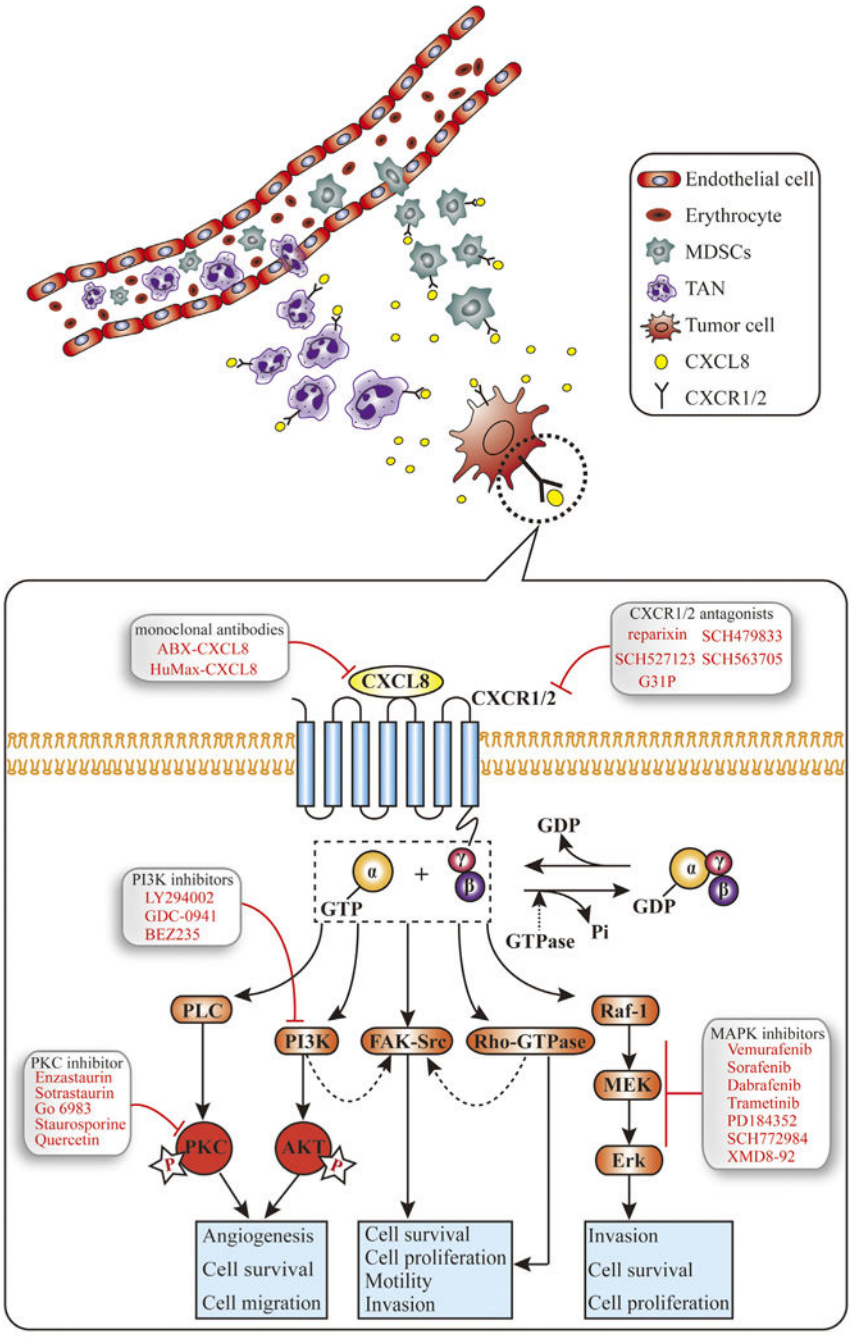

Fig. 2.

The diagram summarizing the major signalling pathways of CXCL8 in cancers. CXCL8 chemoattractant myeloid-derived suppressor cells (MDSCs) and tumour-associated neutrophils (TAN) to tumour microenvironment which are associated with immune suppression. At the celluar level, CXCL8 binds to G protein-coupled receptors (GPCRs), namely CXCR1 or CXCR2, leading to the activation of G protein. Heterotrimeric Ga and bg subunits stimulate the main effectors PLC and PI3K to induce phosphorylation of PKC and Akt, respectively. The two signalling pathways have been reported to activate respective

transcription factors associated to survival, angiogenesis and migration of tumour cells. In addition, CXCL8 activates non-receptor tyrosine kinases (e.g., Src and FAK) and members of the RhoGTPase family, which promote cell proliferation, survival, motility and invasion. Activated Raf-1/MAP/Erk signalling cascade contributes to cell proliferation and survival. Dashed arrows, uncon rmed pathways involved in CXCL8 signalling axis.

Table 1

The role of CXCL8-CXCR1/2 pathway in common cancers.

Cancer type	Function	Associated factors	Ref.
Breast cancer	Proliferation	cyclin D1, $p27^{Kip21}$	[137]
	Angiogenesis	MVD	[7,63,66]
	Metastasis	integrin 3β	[137,138]
	Chemoresistance	MRP	[10]
	CSCs activation	HER2	[64,65]
Prostate cancer	Proliferation	cyclin D1, AR, CXCR7, p53	[23,79,139,140]
	Angiogenesis	VEGF	[8,9]
	Metastasis	MMP-2/9, E-cadherin	[9,141]
	Chemoresistance	src, NF-κB, c-FLIP, Akt	[6,11,142]
Lung cancer	Proliferation	EGFR	[25]
	Angiogenesis	VEGF, MVD	[88,90,143,144]
	Metastasis	PLD, Akt, PKC, MMP-2/9,	[92,93,145,146]
Colorectal cancer	Proliferation	EGFR, MAPK	[107,147,148]
	Angiogenesis	CD31, MVD	[107,121]
	Metastasis	PI3K, Akt, Erk, integrin αvβ6	[108,149,150]
	Chemoresistance	NF-κB, Bcl-2, survivin	[151,152]
Melanoma	Proliferation	Akt, Erk	[105]
	Angiogenesis	MMP-2/9, VEGF	[99,153,154]
	Metastasis	MMP-2	[99]

MRP, Multidrug resistance protein; AR, androgen receptor; Bcl-2, B-cell CLL/lymphoma 2.