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Review

Potential roles and targeted therapy of the CXCLs/CXCR2 axis in cancer and inflammatory diseases

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ABSTRACT

The chemokine receptor CXCR2 and its ligands are implicated in the progression of tumours and various inflammatory diseases. Activation of the CXCLs/CXCR2 axis activates multiple signalling pathways, including the PI3K, p38/ERK, and JAK pathways, and regulates cell survival and migration. The CXCLs/CXCR2 axis plays a vital role in the tumour microenvironment and in recruiting neutrophils to inflammatory sites. Extensive infiltration of neutrophils during chronic inflammation is one of the most important pathogenic factors in various inflammatory diseases. Chronic inflammation is considered to be closely correlated with initiation of cancer. In addition, immunosuppressive effects of myeloid-derived suppressor cells (MDSCs) against T cells attenuate the anti-tumour effects of T cells and promote tumour invasion and metastasis. Over the last several decades, many therapeutic strategies targeting CXCR2 have shown promising results and entered clinical trials. In this review, we focus on the features and functions of the CXCLs/CXCR2 axis and highlight its role in cancer and inflammatory diseases. We also discuss its potential use in targeted therapies.

1. Introduction

Chemokines are a group of low-molecular-weight chemotactic cytokines that are involved in many biological processes, such as leukocyte migration, embryogenesis, angiogenic activity and tumour growth and metastasis [1–3]. Mature chemokines contain 60–100 amino acids. Depending on the location of cysteine at the N-terminus, chemokines can be divided into 4 subtypes: CXC, CC, C, or CX3C. The family of CXC chemokines is further subdivided into the ELR + and ELR- groups based on whether the tripeptide glutamic acid-leucine-arginine (the 'ELR' motif) precedes the cysteine. ELR-CXC chemokines, such as interleukin-8 (IL-8), epithelial cell-derived neutrophil-activating protein-78 (ENA-78) and growth-related oncogene (GRO-α/β/γ), seem to be potent angiogenics, whereas chemokines lacking the ELR motif, such as platelet factor 4, are angiostatic [4]. The receptors that bind to and are activated by these ligands are seven transmembrane-domain G protein-coupled receptors (GPCR). To date, more than 50 chemokines and 19 receptors have been found in human beings [5,6]. Since the 1980s, when IL-8, the first CXC chemokine, was purified from culture supernatant of human monocytes stimulated by LPS and PHA, there have been many studies on IL-8 and its receptors [7–9]. Samanta et al. found two IL-8 receptors: IL-8 RA and IL-8 RB, also known as CXCR1 and

Abbreviation: COPD, chronic obstructive lung disease; MDSCs, myeloid-derived suppressor cells; IL-8, interleukin-8; ENA-78, epithelial cell-derived neutrophil-activating protein-78; GRO-α/β/γ, growth-related oncogene; GPCR, G protein-coupled receptors; VASP, vasodilator-stimulated phosphoprotein; ARDS, acute respiratory distress syndrome; ALI, acute lung injury; PI3K, phosphatidylinositol-3 kinase; PLC, phospholipase C; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; JAK2, Janus kinase; STAT3, signal transducer and activator of transcription; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; MMP-9, matrix metalloproteinase-9; TME, Tumour microenvironment; ECM, extracellular matrix; Tregs, regulatory T cells; PF4, platelet factor 4; CTGF, connective tissue growth factor; CSCs, cancer stem cells; MSCs, mesenchymal stem cells; EPC, endothelial progenitor cells; AML, acute myeloid leukaemia; MDS, myelodysplastic syndromes; hPSCs, human pluripotent stem cells; ICB, immune checkpoint blockade; PD-1, programmed death 1; MIF, macrophage migration inhibitory factor; PMNs, polymorphonuclear neutrophils; PGP, proline–glycine–proline; PBMCs, peripheral blood mononuclear cells; BAL, bronchoalveolar lavage; PAI-1, plasminogen activator inhibitor-1; CF, cystic fibrosis; MS, multiple sclerosis; TBI, traumatic brain injury; AD, Alzheimer's disease; OPCs, oligodendrocyte precursor cells; EAE, experimental autoimmune encephalomyelitis; CSF, cerebrospinal fluid; DCV, delayed cerebral vasospasm; CAD, coronary artery disease; RA, rheumatoid arthritis; SS, systemic sclerosis; SLE, system lupus erythematosus; DM, dermatomyositis; IBD, Inflammatory bowel disease; MDBs, Mallory-Denk Bodies; OIS, oncogene-induced senescence; TLRs, Toll-like receptors; CLP, caecal ligation and puncture surgery

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Table 1
Characteristics of the ligands binding to CXCR2.

Systematic name	Mouse ligands	Human ligands	Chemotaxis	Receptors	Affinity to CXCR2(nm, Kd) [14]
CXCL1	KC	GRO-α, MGSA-α	Neu,EC	CXCR2	5
CXCL2	MIP-2	GRO-β, MGSA-β, MIP-2α	Neu,EC	CXCR2	4
CXCL3	MIP-2	GRO-γ, MGSA-γ, MIP-2β	Neu,EC	CXCR2	1
CXCL5	LIX	ENA-78	Neu,EC	CXCR1,CXCR2	11
CXCL6	CKα-3	GCP-2	Neu,EC	CXCR2	N/A
CXCL7	N/A	NAP-2	Neu,EC	CXCR2	7
CXCL8	N/A	IL-8	Neu,basophils, EC,monocytes	CXCR1,CXCR2	4

These ligands all have ELR motif and are able to promote angiogenesis.
Neu: Neutrophils; EC: Endothelial cells.

CXCR2 [10]. CXCR2 belongs to the CXCR family and is the major receptor of ELR-CXC chemokines that mediate angiogenesis [11]. It is expressed in various cell types, such as neutrophils, monocytes, eosinophils, endothelial cells, mast cells and oligodendrocytes [12]. According to analysis of human peripheral blood leukocytes, CXCR1 and CXCR2 are expressed on neutrophil with the highest level, at an approximately equal ratio. Whereas monocytes express CXCR2 at a higher level than CXCR1 [13]. CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8 are the known ligands of CXCR2 [14] (Table 1). The CXCLs/CXCR2 axis induces the migration of immunocytes and angiogenesis in tissues, which is important for tumour progression, inflammation and a variety of diseases.

CXCR2 belongs to GPCR, which is a large family that contains more than 800 receptors in humans and is related to numerous human diseases. It is estimated that 30–40% of all drugs on the market target GPCRs [15]. To date, the structures of several human GPCRs have been identified, including chemokine receptor CXCR1 [16]. CXCR2 shares 78% sequence homology with CXCR1, and they both bind to IL-8 with similar affinity (K_d of approximately 4 nM) [14,17]. However, CXCR1 only binds to CXCL6 and CXCL8, which indicates CXCR2 interacts with more ELR+ chemokines with higher affinity and plays a more vital role in chemotaxis of cells [18]. The seven transmembrane structure includes one N-terminus, one C-terminus, three extracellular and three cytosolic loops. The N-terminus of CXCR2 is outside the cell, whereas the C-terminus is inside the cell and contains serine and threonine residues to aid in the phosphorylation, internalization and sequestration processes of CXCR2 [19]. Several structural features are essential for ligands binding and function, such as the N-terminal segment and second extracellular loop [20,21]. In a C-terminal truncated CXCR2 mutant, Richmond et al. found that the LLKIL (Leu-Leu, Leu-Ile, and Ile-Leu) motif at the carboxyl terminus is required for sequestration and ligand-mediated chemotaxis of CXCR2 [22]. Vasodilator–stimulated phosphoprotein (VASP), a kind of cytoskeleton–associated protein, directly interacts with the C-terminus of CXCR2, which is essential for mediating leukocyte migration [23] (Fig. 1).

CXCLs/CXCR2 signalling plays a vital role in both cancer and various inflammatory diseases, such as chronic obstructive lung disease (COPD), asthma, acute respiratory distress syndrome (ARDS)/acute lung injury (ALI), auto-immune diseases. Upregulation of CXCR2 and increased neutrophil/monocyte migration have a close relationship with chronic inflammation and cancer. Studies have increasingly focused on using CXCR2 antagonists in therapeutic strategies for cancer

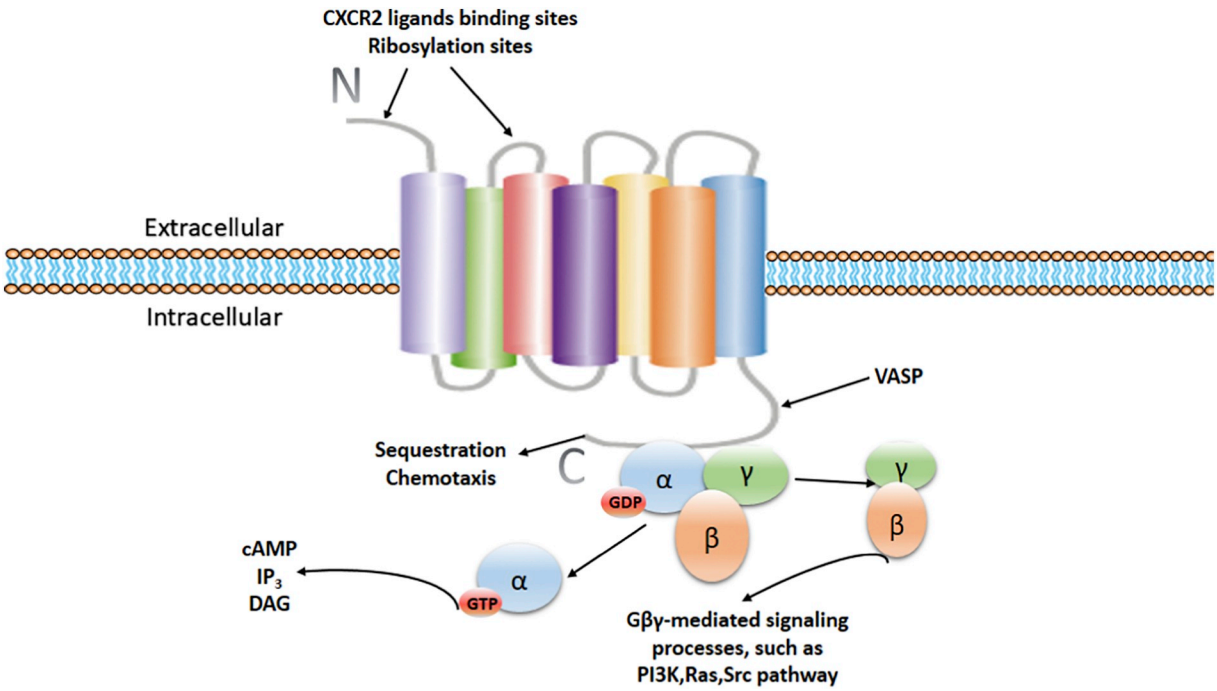

Fig. 1. The Structure of CXCR2. The N-terminal segment and second extracellular loop are essential for ligands binding. The C-terminus contains serine and threonine residues to help with phosphorylation, internalization and sequestration processes. Proteins, such as vasodilator-stimulated phosphoprotein (VASP), also binds to C-terminus of CXCR2. CXCR2 is in complex with a Gαβγ. Following ligands binding, α subunit with GDP changes into α-GTP and disassociates with βγ subunit. Activation of Gα leads to cAMP synthesis and activates phospholipase C (PLC), which then cleaves phosphatidylinositol (4,5)-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol (1,4,5)-trisphosphate (IP_3). Whereas, Gβγ activates G protein-associated signaling.

and related diseases [18,24]. Hence, in this review, we summarize the roles that CXCR2 plays in different diseases and provide a better understanding of the mechanism underlying CXCR2 signalling.

2. CXCR2 ligands

CXCL1, 2, 3, 5, 6, 7 and 8 are all ELR$^+$ CXC chemokines which are known to be angiogenics, and they not only help deliver oxygen and nutrients to tumour tissues but are also constituents of the vascular network and enhance the invasive properties of tumours [25]. CXCR2 deficiency in a murine model further demonstrates increased necrosis and reduced vascular density [26]. Further, CXCR2 expression in tumour cells indicates a poor prognosis and promotes tumour invasion and metastasis [27]. Therefore, the CXCLs/CXCR2 axis is proved to play an essential role in tumour angiogenesis, growth, metastasis and even chemoresistance by interacting with multiple tumour factors, including the tumour microenvironment, cancer stem cells and immune checkpoints (Table 2). On the other hand, because of their properties of neutrophil chemotaxis, CXCR2 ligands have been identified important in the pathogenesis of various inflammatory diseases (Table 3).

2.1. CXCL1, 2, 3(GRO-α, β, γ)

In human, CXCL1, 2, 3 are the production of GRO family. They are also known as MGSA for melanoma growth-stimulatory activity. CXCL2 and CXCL3 are 90% and 86% identical in amino acid sequence with CXCL1 [28]. Continuous expression of these three chemokines improves tumour cells survival via stimulating angiogenesis [29]. The expression of CXCL1 and 2 in a tumour microenvironment attracts myeloid-derived suppressor cells (MDSCs) to the tumour, where chemokines that enhance cancer cell survival are produced. Treatments with chemotherapeutic agents lead to the production of TNF-α, which, in turn, increases CXCL1/2 expression in the paracrine axis, resulting in tumour chemoresistance and progression [30]. Meanwhile, CXCL1 has been proved to bind to not only CXCR2 but also to the GPCR encoded by the tumorigenic Kaposi's sarcoma-associated herpes-virus (KSHV)-8 [31]. Overexpression of CXCL1 leads to reduction of fibulin-1, which facilitates cancer cells invasion and metastasis [32]. It has been demonstrated that CXCL3 is responsible for migration of cerebellar granule neuron precursor cells and targeting CXCL3 may represent a novel therapy for medulloblastoma [33]. Autocrine and paracrine of these chemokines can promote cancer cell vascular invasiveness and blockade of CXCR2 can apparently reduce tumour invasion [34].

2.2. CXCL5

CXCL5 is also known as epithelial-derived neutrophil-activating peptide 78 (ENA-78) and upregulated in various cancers [35,36].Meanwhile, the expression of CXCL5 is correlated with cancer staging [37]. It Depletion of CXCL5 in a human non-small cell lung cancer (NSCLC) model inhibits tumour angiogenesis and attenuates both tumour growth and metastasis [35]. Overexpression of CXCL5 in human pancreatic cancer is significantly correlated with poor tumour differentiation, advanced clinical stage, and shorter patient survival (25.5 months shorter than that of patients with low CXCL5 expression) [36]. Interestingly, though CXCL5 plays a negative role in tumorigenesis, it has been shown CXCL5 acts as a protective role in atherosclerosis via modulating macrophage foam cell formation [38].

2.3. CXCL6

CXCL6 is also known as granulocyte chemotactic protein 2 (GCP-2). CXCL6 is originally identified from osteosarcoma cells and shares 67% similar at the amino acid level with CXCL8 [39]. Upregulation of CXCL6 has been observed in multiple tumour cell lines and mesenchymal cells [40]. After stimulating of inflammatory factors or hypoxia, expression level of CXCL6 is also upregulated [41]. CXCL6 Intravenous injection provokes an immediate granulopenia. Staining of CXCL6 in gastrointestinal malignancies correlates with the expression of matrix metalloproteinase-9 (MMP-9/gelatinase B), and together, they promote tumour invasion [42].

2.4. CXCL7

CXCL7 is cleavage product of the platelet a-granule component platelet basic protein (PBP) and connective tissue-activating peptide III (CTAP-III) [43]. It is also known as neutrophil-activating peptide-2 (NAP-2).

After platelets activation, the expression of CXCL7 is significantly upregulated [44]. By transfecting MCF10AT cells, a premalignant breast cancer cell line, with CXCL7, the cells ultimately become malignant and have a greatly enhanced invasive ability [45]. Meanwhile, several clinical studies have identified CXCL7 as a biomarker of prediction for early diagnosis of various cancers and prediction of treatment efficacy [46–48].

2.5. CXCL8

CXCL8 (interleukin-8/IL-8) is the most well investigated chemokine among CXCR2 ligands. It is barely detectable in healthy status, but is rapidly induced by pro-inflammatory cytokines such as TNF-α and IL-1, bacterial or viral products, and cellular stress [49].High level of CXCL8 is associated with increased risk and poor prognosis of cancer, which makes it becoming a predictor of cancer prognosis [50]. Increased expression of CXCL8 has been identified in various cancers, such as breast cancer, prostate cancer, lung cancer, melanoma, colorectal cancer and pancreatic cancer [51–55]. Stimulation of CXCL8 can directly reduce endothelial cells (ECs) apoptosis and enhance ECs proliferation. This angiogenic process is modulating by producing matrix metalloproteinases (MMPs) to break down the extracellular matrix (ECM) which result in formation of vessels in tumour microenvironment [56]. In addition, CXCL8 is also associated with tumour chemoresistance. After administration of oxaliplatin, CXCL8 is up-regulated in prostate cancer cells and reduces cell apoptosis via NF-κB signalling [57]. When inhibition of CXCLs/CXCR2 signalling, the efficacy of anticancer agents can be improved by several folds [58].

3. Signalling pathway of the CXCLs/CXCR2 axis

CXCR2 is a typical GPCR, and the ligands that bind to CXCR2 can activate multiple G-protein-mediated signalling cascades, including the phosphatidylinositol-3 kinase (PI3K)/Akt, phospholipase C (PLC)/protein kinase C (PKC), and mitogen-activated protein kinase (MAPK)/p38 pathways (but not JNK), Ras/Erk, and the Janus kinase (JAK2)/signal transducer and activator of transcription (STAT3) signalling pathway. The activation of these pathways can also modulate the expression of cytokines and chemokine, forming a loop to enhance the function of CXCR2 [72,95,145–149]. Since CXCR1 shares 78% sequence homology with CXCR2, they regulate cells in similar signalling way. But CXCR1, not CXCR2, can activate phospholipase D (PLD) and lead to ROS generation and respiratory burst. This different might due to different rate of internalization between CXCR1 and CXCR2, for the latter one with a faster rate. After truncating C-terminus and impairing internalization, CXCR2 can also activate PLD pathway [150,151] (Fig. 2).

These pathways may function differently when CXCR2 is activated. PI3K plays a vital role in regulating neutrophil migration. Using the inhibitors wortmannin and LY294002 to block the PI3K function, Knall et al. found that PI3K activation is required for neutrophil migration but noted that this kind of cell migration is independent of the activation of the ERK and p38 MAPK pathways [152]. AKT is the target of PI3K and is expressed in normal and cancer cells. PI3K/AKT pathway is one of the most common changes during human malignancy [153]. It participates

Table 2
Biological properties of CXCR2 ligands in cancer.

Ligands	Condition	Biological properties
CXCL1	Breast cancer	CXCL1 is correlated with migration and invasion of cancer cells and is especially overexpressed in triple negative breast cancer (TNBC); Meanwhile, CXCL1 is increased in paclitaxel and doxorubicin-treated mammary tumor cells which is associated chemoresistance [59–62].
	Colorectal cancer(CRC)	High expression of CXCL1 is observed in CRC patients with down-regulation of the matrix protein fibulin-1, promoting tumour cells proliferation and angiogenesis. The level of CXCL1 is also associated with prognosis of CRC patients. Down-regulation of CXCL1 results in a nearly complete prevention of tumor growth in nude mice [32,63,64].
	Esophageal carcinoma	CXCL1 is significantly elevated, which is produced by cancer-associated fibroblasts and promote cancer progression in a ROS-dependent manner; CXCL1/CXCR2 proliferation signaling is also dependent on NF-KB and early growth response-1(EP-1) [65,66].
	Lung cancer	CXCL1 is significantly increased in lung cancer and knocking-down of CXCL1 hinders tumour growth [67].
	Melanoma	CXCL1 and CXCL8, but not CXCL2, CXCL3 and CXCL5 are increased in human melanoma cell lines with increased IkappaB kinase (IKK) activity; recombinant CXCL1 can directly induce IKK activity, whereas inhibition of IKK activity results in down-modulation of CXCL1 [68].
	Ovarian cancer	CXCL1 is increased in ovarian cancer via GRB2-associated binding protein 2-dependent autocrine way, promoting tumour cells proliferation and angiogenesis; production of CXCL1 is also regulated by lysophosphatidic acid (LPA), a glycerol backBone phospholipid mediator present in serum and ascites of ovarian cancer patients [69,70].
	Pancreatic ductal adenocarcinoma(PDA)	CXCL1 is robustly expressed in human PDA and highly expressed in mouse PDA, which can also be induces by chemotherapy [71].
CXCL2	Bladder cancer	Expression of CXCL2 promotes recruitment of MDSCs, resulting in tumor progression [72].
	Esophageal carcinoma	Knock-down of CXCL2 and its downstream factor EGR1 reduces cisplatin-induced cell apoptosis in esophageal cancer cells [73].
	Hepatocellular carcinoma(HCC)	CXCL2 is up-regulated in the blood of HCC patients which enhances HCC cell proliferation and metastasis [74].
	Ovarian cancer	CXCL2 is increased in ovarian cancer via GRB2-associated binding protein 2-dependent autocrine way, promoting tumour cells proliferation and angiogenesis [69].
	PDA	CXCL2 is increased in stromal cells of PDA [75].
CXCL3	Esophageal carcinoma	CXCL3 is significantly elevated in esophageal carcinoma [76].
	Medulloblastoma	CXCL3 is involved in migration of cerebellar granule neuron precursor cells (GPCs). Deficiency of CXCL3-induced GPCs may result in higher frequency of medulloblastoma in Patched1 heterozygous mice [33].
CXCL5	Breast cancer	CXCL5 can be produced by mesenchymal stem cells of breast cancer and contributes to breast cancer cell line migration, resulting in cancer metastasis; CXCL5 is markedly secreted by breast tumor-associated osteoblasts via increased Raf/MEK/ERK activation; CXCL5 may be a potential indicator for breast cancer metastasis, especially bone metastasis [60,77].
	Cholangiocarcinoma	Cholangiocarcinoma cell lines produce CXCL5 that promotes their invasion and migration in an autocrine manner; Meanwhile, high-expression of CXCL5 is associated with poor prognosis of patients with curative hepatic resection [78].
	Lung cancer	CXCL5 is elevated in human lung cancer and strongly associated with vascularity of the tumors, contributing to metastasis of cancer cells and tumor progression; Cyclooxygenase-2(Cox-2) enhances lung tumor progression via increasing CXCL5 and CXCL8 expression [35,79].
	Gastric cancer	Level of CXCL5 is associated with late stage of gastric cancer. CXCL5 expression is positively correlated with N stage, whereas don't correlated with T stage [37].
	Pancreatic cancer	Overexpression of CXCL5 is correlated with poor prognosis of pancreatic cancer; CXCL5 is elevated in tumour cells of PDA and is the most prominently expressed CXCR2 ligand in human PDA. CXCL5 expression is associated with mutant Kras expression and is regulated by NF-κB activation [36,75].
	Prostate cancer	CXCL5 is highly expressed in androgen-independent prostate cancers, and is responsible for cell migration and epithelial-to-mesenchymal transition; Regulation of CXCL5 is in a nonautonomous way via the Hippo-YAP pathway and contributes to MDSCs recruitment in cancer tissues [80,81].
CXCL6	Lung cancer	Upregulation of CXCL6 is identified in small cell lung cancer instead of non-small cell lung cancer. Expression of CXCL6 is correlated with tumor progression, especially under unfavorable condition such as oxygen deprivation [41].
	Gastrointestinal tumors	Expression of CXCL6 promotes tumor progression via angiogenesis and enhances tumor invasion and metastasis via attracting neutrophils [42,82].
CXCL7	Breast cancer	Transfecting premalignant breast cancer cells with CXCL7 leads to become as malignant and invasive as malignant breast cancer cells [45].
	Cholangiocarcinoma	High expression of CXCL7 is correlated with poor differentiation, lymph node metastasis, vascular invasion and advanced clinical stage in patients with cholangiocarcinoma [81].
	Hepatoblastoma	CXCL7 is increased in patients with hepatoblastoma and is correlated with clinical stage, lymph node metastasis, vascular invasion and serum AFP level, and thereby it might be a promising factor for prognosis and diagnosis of hepatoblastoma [83].
	Lung cancer	CXCL7 is upregulated in non-small cell lung cancer and can be regarded as biomarker for early diagnosis of lung cancer [46].
	Renal cell carcinoma	CXCL7 is a potential predictive marker of diagnosis and sunitinib efficacy in patients with renal cell carcinoma [47,48,83].
CXCL8	Breast cancer	CXCL8 promotes osteoclastogenesis and bone resorption and is much higher in breast cancer patients with bone metastasis; Meanwhile, proteasome inhibition (bortezomib or carfilzomib) increases CXCL8 expression in triple negative breast cancer and inhibition of IKK significantly decreases proliferation, migration, and invasion of proteasome inhibitor-treated TNBC cells [51,84].
	Colorectal cancer	High level of CXCL8 is correlated with advanced stages of colorectal cancer; Overexpression of CXCL8 promotes colon cancer cells proliferation and EMT via PI3K/Akt/NF-κB signaling pathway; CXCL8 is markedly increased in chemoresistance colorectal cancer cell lines [50,85,86].
	Esophageal carcinoma	CXCL8 is significantly elevated in esophageal carcinoma [76].
	Glioma	CXCL8 is increased in advanced histological grade glioma [87].
	Leukemia	The average level of CXCL8 is much higher in patients with acute myeloid leukemia and CXCL8 is also a positive recurrence indicator [88].
	Lung cancer	CXCL8 stimulates cancer cells proliferation in a dose-dependent manner via epidermal growth factor receptor transactivation [52].
	Melanoma	CXCL8 can be produced by melanoma cell lines and is elevated in patients serum, correlating with tumor load; Up-regulation of CXCL8 depends on loss of tristetraprolin(TTP); Following treatment with BRAF inhibitor, CXCL8 secretion is decreased with increases in cytotoxic tumor-infiltrating T cells in corresponding tumor biopsies [89,90].

(*continued on next page*)

Table 2 (*continued*)

Ligands	Condition	Biological properties
	Ovarian cancer	CXCL8 is increased in ovarian cancer via GRB2-associated binding protein 2-dependent autocrine way, promoting tumour cells proliferation and angiogenesis; Proteasome inhibition increases CXCL8 expression in ovarian cancer via activation of IKKβ and EGR-1 which might be the mechanism limits efficacy of bortezomib in ovarian cancer [69,91].
	Prostate cancer	CXCL8 is upregulated following chemotherapy administration and reduces cell apoptosis, resulting in chemotherapy resistance; In PTEN-deficient prostate cancer, CXCL8 expression and signaling is enhanced and augments stroma-derived CCL2-promoted proliferation and CXCL12-mediated invasion [53,57,92].
	Pancreatic cancer	CXCL8 promotes pancreatic cells proliferation, and CXCL8 is significantly increased in Gemcitabine-treated PDAC and associated with neovascularization [55,93].
	Thyroid cancer	Aberrant thyroid-stimulating hormone increases CXCL8 secretion of poorly differentiated thyroid cancer, promoting angiogenesis and cell growth [94].

in modulating cell survival, angiogenesis and motility. Abnormal regulation of the CXCR2 phosphorylation also leads to activation of the MAPK pathway, including the phosphorylation of ERK and p38 but not of JNK, and this process is MyD88-dependent [72,152]. The activation of MAPK signalling is associated with cell proliferation and survival. Another downstream target is the phosphorylation of PLC, which is src-family-dependent. Activated PLC produces two secondary messengers, IP3 and DAG, leading to PKC phosphorylation and an oscillation of the cytosolic calcium concentration, which affects cellular metabolism and function [154,155]. Interaction between receptors is a common phenomenon during signal transduction. Epidermal growth factor receptor (EGFR) is known to have cross-talk with GPCRs, and there is an intracellular mechanism of transactivation [156]. The binding of CXCL8 to CXCR2 results in the transactivation of EGFR, which is partially responsible for angiogenesis and cell migration, and this process is cathepsin B-dependent. Inhibition of cathepsin B blocks the CXCL8-induced migration of endothelial cells [157]. Increased transcriptional activity of NF-κB is also observed when CXCR2 is activated. NF-κB is a transcription factor that regulates the expression of various cytokines and chemokines, including CXCL1, 2, 3 and 8, and initiates both extracellular and intracellular regulatory events [158]. Wang et al. proved that the upregulation of NF-κB is dependent on the MEKK1, MEK3/6, and p38 pathways, whereas the MEK1/ERK pathway has no effect on NF-κB activity [159]. Further, the PI3K/AKT pathway activated by CXCR2 promotes NF-κB binding to nuclear DNA and transcriptionally regulates cellular proliferation, apoptosis and functioning. Inhibition of CXCR2 or IKB attenuates the expression of Bcl-2 and survivin, leading to increased apoptosis in cancer cells [160]. CXCR2 signalling also initiates a delayed onset of Rac GTPase activity and affects cell retraction, resulting in the formation of gaps between cells [161]. Migratory responses and proliferation of CXCR2-expressing cells are also mediated via the JAK2-STAT3 pathway in a paracrine or autocrine manner at high chemokine levels [147].

4. CXCLs/CXCR2 axis in cancer

The growth and progression of tumours require support from the surrounding stromal microenvironment, such as tumour-associated fibroblasts, leukocytes, bone marrow-derived cells, and blood and lymphatic vascular endothelial cells [162]. High levels of CXCR2 expression are observed in both the stroma and epithelium in a model of pancreatic cancer [163]. Various studies have observed increased CXC chemokine expression via the autocrine and paracrine pathways in different types of tumours, indicating that these chemokines are associated with tumour growth and metastasis. Chemokines for CXCR2, including CXCL1, 2, 3, 5, 6, 7 and 8, are secreted and expressed in different kinds of cancer, including solid tumours (melanoma, breast, lung, bladder, pancreatic, liver, prostate and colorectal cancer) and haematological malignancies (AML, Hodgkin's lymphoma). They are powerful neutrophil chemoattractant and associated with tumour angiogenesis, progression and chemoresistance [45,164–167] (Fig. 3).

4.1. The regulation of CXCLs/CXCR2 axis in tumour microenvironment (TME)

In addition to malignant cells, the emergent TME is composed of extracellular matrix (ECM) and multiple types of non-malignant cells, including fibroblasts, blood and lymphatic endothelial cells, mesenchymal stem cells and a great variety of infiltrating leukocytes and the inflammatory mediators that they secrete [168]. TME can induce a variety of stresses to enhance a response of surrounding cells, resulting in upregulated cytokines and chemokines. For instance, under the stimuli of hypoxic and various cellular stresses, an increased secretion of CXC chemokines, such as CXCL8, is observed in gliomas, which correlates with the histological grade in glial neoplasms [87]. Meanwhile, the infiltrating immune cells have the ability to either block tumour development by activating anti-tumour leukocytes, such as $CD8^+$ T cells and M1 macrophages, or promote carcinogenesis, tumour progression and metastasis through immunosuppressive cells, such as regulatory T cells (Tregs) and MDSCs. In this situation, chronic leukocyte infiltration is usually considered a key risk to the balance of immune surveillance [169]. Myeloid cells are essential in both innate and adaptive immune systems, but TME can change them into immunosuppressive cells. Neutrophils and MDSCs are two major myeloid-derived cell groups that function in the interaction between cancer and the CXCLs/CXCR2 axis.

Neutrophils account for 50–70% of all white blood cells in human peripheral blood and are known for their role in defence of microorganisms. Similar to macrophages, tumour-associated neutrophils are divided into anti- and pro-tumour phenotypes [170], but pro-tumour neutrophils usually hold a more prominent position in cancer progression and are associated with aggressive cancer types and worse clinical outcomes [171]. The CXCLs/CXCR2 axis is essential for neutrophil recruitment, and neutrophils lacking CXCR2 are preferentially retained in bone marrow [172]. This chemotaxis process is dependent on the structure of the ELR motif. When the ELR sequence is introduced at the N-terminus of platelet factor 4 (PF4/CXCL4), the modified protein gains the ability of neutrophil activation and thus becomes a neutrophil attractor [173]. In addition to neutrophil recruitment, this signalling pathway leads to neutrophil activation. An intratumoral injection of CXCL6 correlates with a strong influx of tumour-associated neutrophils and the increased expression of gelatinase-B, a major secreted matrix metalloproteinase (MMP-9) from neutrophils, leading to increased angiogenesis and tumour growth [82]. Gelatinase-B can truncate IL-8 and increase the ability of neutrophil activation 10- to 27-fold [174]. This process indicates that there is a positive feedback loop between CXC chemokines and CXCR2. The neutrophils that infiltrate tumour tissues are also associated with the status of CD8 (+) T cells. A depletion of neutrophils in tumour-bearing animals leads to an increase in activated CD8 (+) T cells and shows an increased anti-tumour effect [170].

MDSCs are known as a group of immature immunosuppressive cells that expand during cancer, inflammation and infection, and their remarkable function is suppressing T cell response [175]. It is accepted

Table 3
Biological properties of CXCR2 ligands in inflammatory diseases.

Ligands	Condition	Biological properties
CXCL1	AD	CXCL1 is elevated in Alzheimer disease (AD) patients' cerebrospinal fluid [95,96].
	ARDS	CXCL1 is increased and correlated with neutrophil activation and accumulation in patients with acute respiratory disease syndrome (ARDS) [97].
	Asthma	Airway smooth muscle (ASM) only produces CXCL1 in an asthma model, inhibition of CXCL1 reduces mast cell migration [98].
	Atherosclerosis	CXCL1 is increased via HIF-1α/miR-19a pathway with monocytes accumulation [99].
	Arthritis	Elevated level of CXCL1 with obvious neutrophils infiltration is observed in patients with arthritis [100].
	Alcoholic hepatitis	CXCL1 is produced by hepatocytes and hepatic stellate cells and is significantly increased [101].
	AKI	CXCL1 is significantly increased in ischemic acute kidney injury (AKI). Less CXCL1 is associated with protection against ischemic in murine model [102].
	COPD	Enhanced interaction between CXCL1 and CXCR2 with high level of CXCL1 in chronic obstructive pulmonary disease (COPD) patients [103,104].
	Cardiac hypertrophy	CXCL1/CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy via monocytes infiltration [105].
	IBD	CXCL1 is slightly increased in patients with inflammatory bowel disease (IBD) [106,107].
	Liver fibrosis	CD147 promotes CXCL1 secretion with hepatic stellate cells (HSCs) activation, resulting to liver fibrosis [108].
	Multiple sclerosis	Histological studies suggest CXCL1 is increased around the peripheral areas of demyelination;CXCL1/CXCR2 might be a novel mechanism for recruitment of oligodendrocytes to areas of damage for lesion repair; Experimental autoimmune encephalomyelitis (EAE) is an animal model of MS, elevated CXCL1 is observed at the onset of EVE and expressed in astrocyte [109–111].
	Nociception	CXCL1 and neutrophils induced by CXCL1 are involved in pathological pain condition; Opioids enhances CXCL1 expression and function, leading to mechanical hypersensitivity in mice; Spinal application of CXCL1 not only elicited pain hypersensitivity but also induced rapid neuronal activation [112–114].
	Psoriasis	CXCL1 is increased and can be produced by vessel-associated cells in patients with psoriasis [115,116].
	Sjogren's syndrome	CXCL1 and CXCR2 are overexpressed in patients with Sjogren's syndrome and contribute to inflammation and neovascularization [117].
	Systemic sclerosis	CXCL1 is elevated in systemic sclerosis (SSc) patients' serum and usually correlated with damage of internal organs, especially pulmonary damage [118].
	Type-I diabetes	CXCL1 is increased in type-I diabetes and involved in leukocytes infiltritio [119].
	VOC	CXCL1 is incredibly increased in hemolytic transfusion reactions (HTRs)-induced vaso-occlusive crisis (VOC), meanwhile, recombinant CXCL1 also can induce VOC [120].
CXCL2	Arthritis	Elevated level of CXCL2 with obvious neutrophils infiltratio [100].
	COPD	CXCL2 is increased in COPD patients [104].
	Multiple sclerosis	Transient receptor potential melastatin 2 (TRPM2), a Ca2 + -permeable nonselective cation channel, exacerbates EAE-associated inflammation via increased production of CXCL2 [121].
	Psoriasis	High level of CXCL2 is observed in patients with psoriasis [115,116].
CXCL3	N/A	
CXCL5	Arthritis	CXCL5 is elevated in patients with arthritis with obvious neutrophils infiltration; Combination calcitonin (CT) with glucocorticoids (GC) synergistically reduces CXCL5 expression in experimental arthritis, indicating blocking CXCL5 might contribute to ameliorating disease [122–125].
	Atherosclerosis	CXCL5 is increased in a mouse model of atherosclerosis but is not associated with neutrophils accumulation. In contrast, it acts as a protective role via modulating macrophage foam cell formation [38].
	COPD	Level of CXCL5 is upregulated, especially in patients with acute severe exacerbations [126,127].
	Coronary artery disease (CAD)	Expression of CXCL5 and CXCR2 are significantly increased and associated with increased risk of coronary artery disease; Meanwhile, CXCL5 variant might be a genetic risk factor for the susceptibility of CAD [128,129].
	Neuroinflammation	CXCL5 is markedly increased in the amniotic cavity in response to intrauterine infection and preterm birth in clinical studies and contributes to white matter injury in the immature brain after hypoxic ischemia [130].
	Severe exacerbations of asthma	CXCL5 level is significantly increased in patients with severe exacerbations of asthma and is correlated with accumulation of eosinophil rather than the number of neutrophils [131].
CXCL6	Arthritis	CXCL6 is increased collagen-induced arthritis and associated with severity of arthritis [132].
CXCL7	COPD	Increased monocyte migration in COPD patients is based on enhanced interaction between CXCL7 and CXCR2 rather than different expression of cellular receptors [103].
	Diabetic nephropathy	CXCL7 contributes to glomerular endothelial injury during diabetic nephropathy and using neutralizing anti-CXCL7 antibody can attenuate such injury [133].
CXCL8	ARDS	CXCL8 level is significantly increased in ARDS patients' bronchoalveolar lavage fluid (BAL) and associated with neutrophil activation and accumulation, indicating early appearance of CXCL8 in BAL of patients may be an important prognostic indicator for the development of ARDS [97].
	AD	Expression of CXCR8 is increased in brain tissue and CSF in a time-dependent manner [20,95,96,134].
	Asthma	CXCL8 is increased and regulates cell contraction and migration via Ca2+ release, causing airway structure remodeling. The concentration of CXCL8, but not CXCL1 or CXCL5, is significantly increased in refractory asthma and contributes to neutrophil-induced inflammation [135–137].
	Arthritis	Serum level of CXCL8 is increased in rheumatoid arthritis and enhances osteoblast-mediated osteoclastogenesis, which might contribute to osteoporosis in rheumatoid arthritis [138].
	Alcoholic hepatitis	CXCL8 and CXCR2 are significantly increased in alcoholic hepatitis livers and associated with Mallory-Denk Bodies formation [139].
	COPD	Expression of CXCL8 is upregulated in patients with COPD, especially in exacerbation of COPD [126,127].
	Diabetic Nephropathy	CXCL8 is significantly increased in high-fat diet/streptozocin-induced diabetic mice [140].
	IBD	CXCL8 is significantly increased in colonic mucosa of patients with IBD [141–143].
	Multiple sclerosis	CXCL8 is upregulated in serum of MS patients without receiving interferon-beta therapy [144].
	Psoriasis	High level of CXCL8 is observed in patients with psoriasis, which is correlated with neutrophil accumulation and disease progression. Depletion of neutrophils obviously ameliorates the disease severity [115,116].
	Systemic sclerosis	Serum level of CXCL8 is increased in patients with SSc and correlated with rheumatoid factor positivity [118].

that these cells participate in tumour immunosuppression and promote immune escape [176]. However, it is not clear whether MDSCs are the prerequisite for tumour progression or whether a progressing tumour recruits MDSCs into malignant lesions [177]. Generally, MDSCs in mice are recognized by the coexpression of Gr1 and CD11b and can be further divided into two subtypes: granulocytic ($CD11b^+Ly6G^+Ly6Clow$, PMN-MDSC) or monocytic ($CD11b^+Ly6G^-Ly6Chigh$, M-MDSC) in mice [178]. However, there is no defined marker for MDSCs in humans.

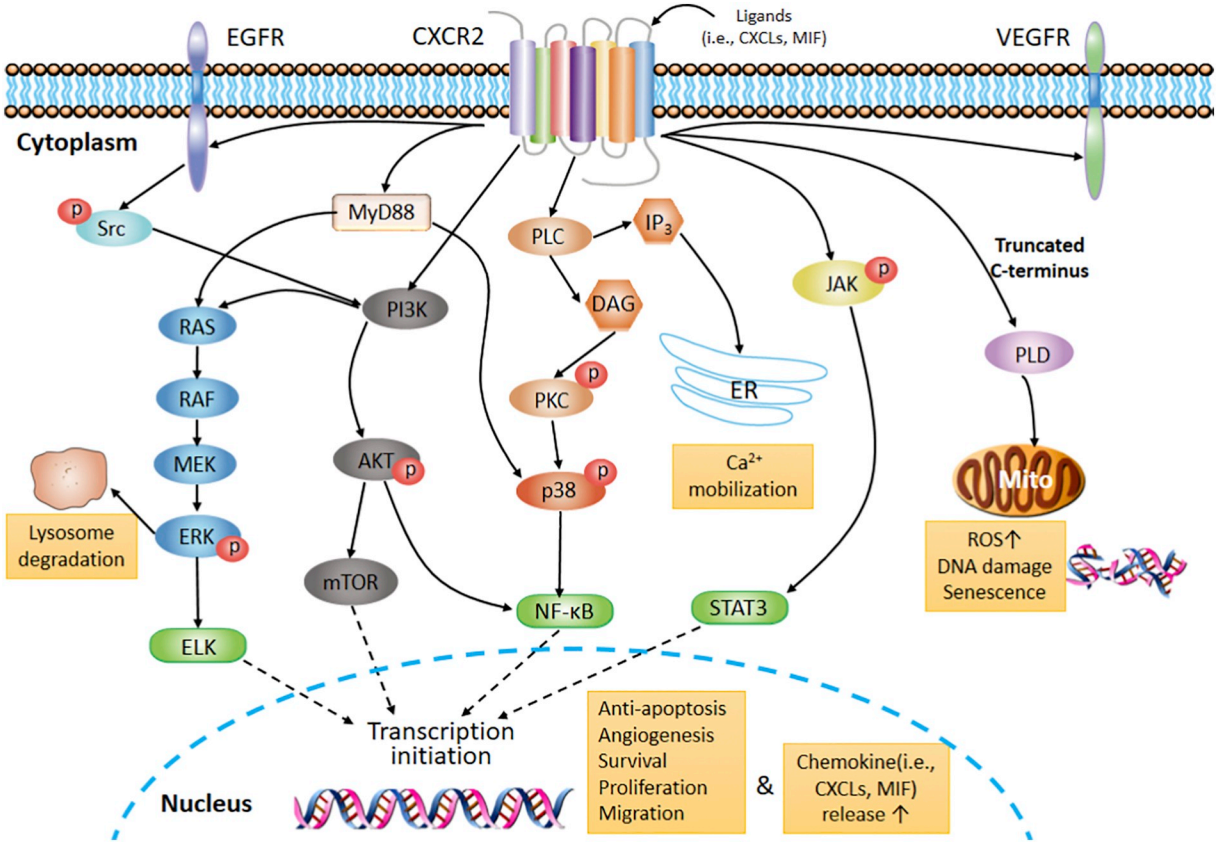

Fig. 2. CXCLs/CXCR2 signal transduction pathway. CXCR2 is a typical GPCR. Its activation leads to transcription of various genes, such as ERK, p38, AKT, JAK2, and modulates cell survival, angiogenesis, proliferation and senescence. Whereas, CXCR2-mediated cell migration is mainly dependent on PI3K/AKT pathway. Activation of CXCR2 also leads to Ca^{2+} mobilization from ER (Endoplasmic Reticulum) and affects cell contraction and morphology. C-terminal truncated CXCR2 is capable of activating PLD and leading to oxidative burst.

Researchers usually consider $CD11b^{+}CD33^{+}HLA\text{-}DR^{-}$ [72,179] or $CD66b^{+}$ $CD11b^{+}$ [180,181] to be granulocytic MDSCs in humans. CXCL1 and CXCL2 attract MDSCs into the tumour and then produce chemokines, including S100A8/9, that can enhance cancer cell survival. Whereas chemotherapeutic agents kill cancer cells, these treatments trigger a parallel stromal reaction that leads to TNF-α production by endothelial and other stromal cells. TNF-α heightens the expression of CXCL1/2 in cancer cells, thus amplifying the CXCL1/2-S100A8/9 loop and causing chemoresistance [30]. The expression levels of CXCR2 in MDSCs from the peripheral blood and tumours of bladder cancer patients are significantly higher than the levels of healthy people [72]. However, another study found that compared to normal mature neutrophils in the peripheral blood, PMN-MDSCs expresses less CXCR1 and CXCR2, which contributes to reduced apoptosis and migration and results in peripheral immunosuppression in cancer patients [181]. Myelocytes from bone marrow of tumour-bearing mice express more CXCR2 than do those of normal mice, which causes the migration of myelocytes to the tumour [182,183]. However, M-MDSCs are more immunosuppressive than PMN-MDSCs are [184]. In human studies, M-MDSCs but not PMN-MDSCs are directly correlated with the suppression of $CD8^{+}$ T lymphocyte activation [185].

Human vascular endothelial cells constitutively express CXCR2. After co-culturing with CXCL8, an increased level of Bcl-2 is observed, which indicates the survival of endothelial cells. Then, endothelial cells begin to secrete matrix metalloproteinases (MMPs) to break down the extracellular matrix (ECM), resulting in angiogenesis [56,186]. Anti-CXCL8 or CXCR2 blockade results in the reduced migration of endothelial cells and decreased MMP-2 production [187]. A combination of CXCL8 and CXCR2 leads to an increased gelatinase B level, as mentioned above, and this protein is important for remodelling the extracellular matrix and for the migration of normal and tumour cells, resulting in a preferable environment for tumour growth and metastasis [188]. Connective tissue growth factor (CTGF), a profibrotic and tumour-promoting factor that is expressed at the tumour-stromal border, can be strongly induced when fibroblasts are co-cultured with CXC chemokines, and this process is CXCLs/CXCR2-dependent [163]. Injection of a mixture of tumour cells and tumour-associated fibroblasts shows faster growth rate than that of tumour cells alone. Additionally, CXCR2 inhibition or CXCR2 knockdown in fibroblasts can significantly delay tumour progression [163,189].

4.2. CXCLs/CXCR2 axis in maintaining and migration of Cancer stem cells (CSCs)

CSCs are essential in the onset and metastasis of almost all types of cancers. Recent studies suggest that the CXCLs/CXCR2 axis may play an important role in tumour progression and metastasis by maintaining and promoting the migration of CSCs. The vascular system in glioblastoma maintains CSCs via the IL-8/CXCR2 signalling. Endothelial cells surrounding these CSCs can not only secrete CXCLs but also upregulate CXCR2 expression in CSCs, which enhances CSC migration and growth [190]. Increased CXCR2 expression is also found in lung CSCs [191]. The CXCR1 blockade can reduce the CSC population in breast cancer and retard tumour growth and metastasis, but this effect is not observed for CXCR2 inhibition [59]. However, mesenchymal stem cells (MSCs) seem to play a vital role in the migration of mammary cancer cells via CXCLs/CXCR2 signalling. Inhibition of CXCR2, CXCL1 or CXCL5 significantly abrogates the migratory effect of the mammary cell line to MSC-conditioned media [59,60]. CXCR2 is also highly expressed in stem cells of acute myeloid leukaemia (AML) and myelodysplastic

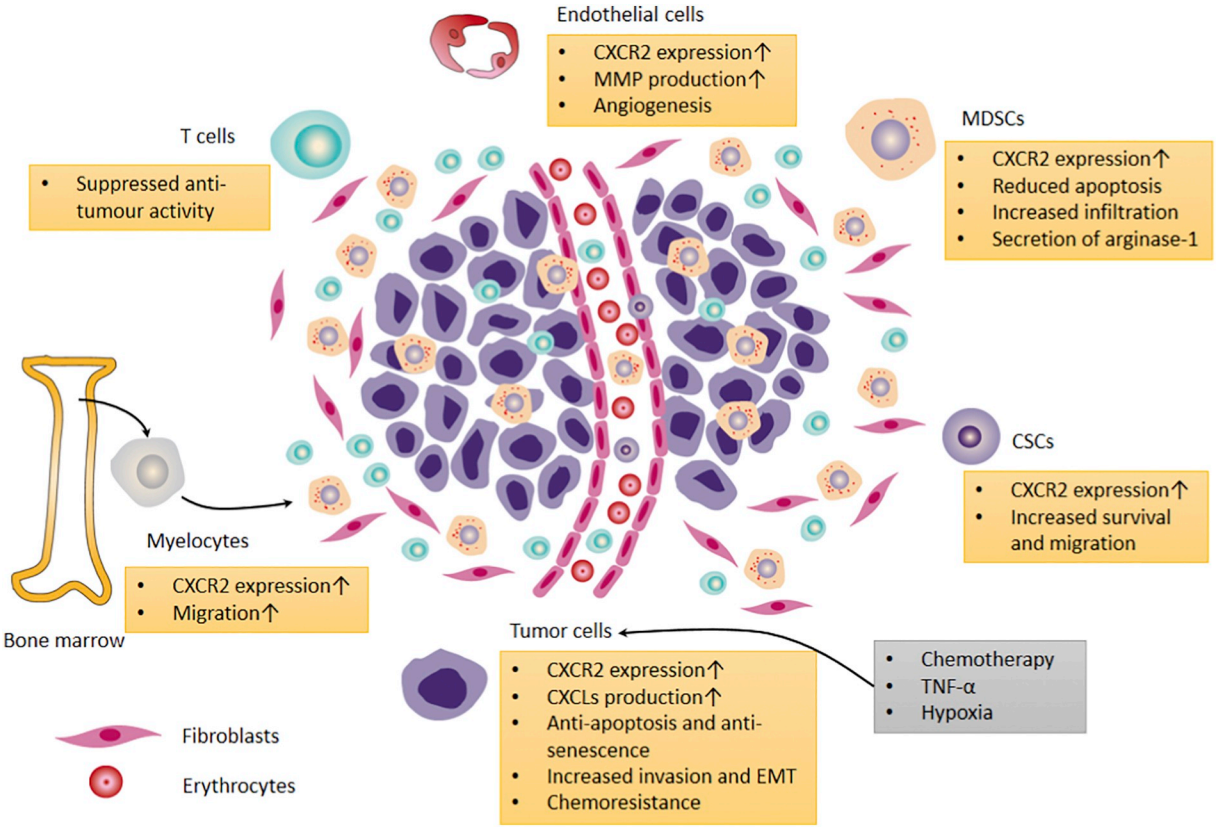

Fig. 3. CXCR2 is involved in tumor development and progression. The expression of CXCR2 is up-regulated on endothelial cells, CSCs and myelocytes following tumour stimuli, which result in angiogenesis, cell survival and migration. Tumor cells express higher level of CXCR2 and more CXCLs due to various cell stresses (i.e. chemotherapy, TNF-α, hypoxia), recruiting more MDSCs into tumor microenvironment and helping with tumour cells survival and invasion. Extensive infiltrated MDSCs release arginase-1 directly impair anti-tumor effect of T cells.

syndromes (MDS). High CXCR2 expression correlates with worse clinical outcomes [192]. CXCLs/CXCR2 signalling can regulate the homing and angiogenesis of endothelial progenitor cells (EPC), and disrupting this interaction results in a decrease in angiogenesis of EPC in mice [193]. Suppressing CXCR2 in human pluripotent stem cells (hPSCs) leads to the decreased expression of pluripotency-associated genes OCT-4, Nanog and Rex-1, indicating that CXCR2 correlates with hPSC self-renewal [194].

4.3. CXCLs/CXCR2 axis regulates tumour cells proliferation, senescence and apoptosis

CXCR2 is not only expressed in leukocytes and endothelial cells, but also a negative indicator on tumour cells. Up-regulation of CXCR2 in tumour cells is a poor prognostic factor in multiple cancers, such as prostate cancer, non-small cell lung cancer, breast cancer [27,195,196]. CXCR2 expression on tumour cells induced by hypoxia in tumour environment is in a time-dependent manner, which contributes to tumour cells survival advantage via HIF-1 and NF-κB signalling [195]. Higher level of CXCR2 is observed in survival malignant cells following chemotherapy and radiotherapy. Knockdown CXCR2 expression in tumour cells can enhance the efficacy of paclitaxel and significantly reduce lung metastases [62]. Using CXCR2 inhibitor decreases tumour cells invasion in human NSCLC and breast cancer cell line [27,197]. CXCR2 is also involved in cell senescence. Studies has found CXCR2 promote anti-apoptosis and anti-senescence in breast cancer cells [197]. Whereas another study has found cells undergoing oncogene-induced senescence (OIS) secrete multiple CXCR2-binding chemokines and coordinately upregulates CXCR2 expression, which reinforce cells growth arrest [198]. This process is still under debate. Meanwhile, high level of CXCR2 is associated with low expression of E-cadherin, and β-catenin in cancer tissue, indicating CXCR2 participate in tumour epithelial-to-mesenchymal transition (EMT) [197].

4.4. Immune checkpoint blockade and the CXCLs/CXCR2 axis

Many studies have proved that MDSCs play a vital role in protecting tumours from the cytotoxic T-cell-mediated anti-tumour effect and suppress the efficacy of immune checkpoint blockade (ICB) [199]. Programmed death 1 (PD-1) on T cells and infiltration of MDSCs seem to be the major factors of tumour immune escape. Early treatment with anti-PD1 can prevent tumour growth, but a delayed treatment shows less benefit, which is associated with an increase in MDSCs [200]. Ipilimumab, an anti-CTLA4 agent, significantly improves the overall survival of stage III/IV melanoma patients. However, patients with greater MDSC infiltration show limited responses to this drug [201,202]. CXCR2 signalling is known to recruit MDSCs to the tumour microenvironment and suppress the anti-tumour effect of T cells. Blockade of CXCR2 significantly reduces the infiltration of MDSCs and improves the function of cytotoxic T cells. A combination of CXCR2 and PD-1 inhibitor demonstrates an obvious anti-tumour effect and increases the overall survival in a murine model [72,80,203]. In addition to CXC chemokines, cytokines such as macrophage migration inhibitory factor (MIF) can activate CXCR2 and result in MDSC migration. MIF/CXCR2 increases the production of the immune-suppressive enzyme arginase-1 in MDSCs without affecting the proliferation and survival of tumour cells. Blocking CXCR2 or MIF can reduce arginase-1 production and increase the cytotoxic T cell response, which can increase the efficacy of ICB [72,204].

The above results suggest that CXCR2 and its responding ligands are

upregulated during cancer development and have a strong relationship with tumour progression and metastasis. Blockade of CXCLs/CXCR2 signalling is a potential therapy for treating various cancers.

5. Inflammatory diseases and the CXCLs/CXCR2 axis

CXCLs/CXCR2 signalling-associated inflammatory diseases are involved in different systems of the human body, including the respiratory, digestive, cardiovascular and nervous systems. These processes are usually associated with extensive leukocyte infiltration. The leukocytes recruited by chemokines to inflammatory sites are essential for non-specific immune defence. However, the uncontrolled and excessive infiltration of leukocytes destroy the organ structure and cause inflammation-associated diseases [205,206].

5.1. Respiratory diseases

In pulmonary inflammation, the recruitment of polymorphonuclear neutrophils (PMNs) from blood is essential for the defence and pathogen elimination in the alveolar space [207]. However, extensive transmigration of PMNs into the lung interstitium and alveolar space leads to an uncontrolled immune response [206].

CXCR2 is markedly upregulated in airway epithelial cells during an acute exacerbation of COPD, and there is a significant and positive association between the number of neutrophils and CXCR2 expression. Blockade of CXCR2 reduces the influx of neutrophils into the bronchoalveolar lavage (BAL) fluid in a model of mice exposed to cigarette smoke. However, increased CXCL2 and CXCL1 levels are observed after CXCR2 inhibition, which indicates that either they fail to bind to CXCR2 or there is no feedback signal to control their expression [208].

Asthma is also a chronic inflammatory disease in the lung that is characterized by episodes of reversible airflow limitation. The role of neutrophils in stable asthma is not clear, but a marked increase is observed during the late-phase reaction after stimulation or an asthma exacerbation [209]. In severe exacerbations of asthma, the CXCL5, CXCL8, and CXCR2 levels are increased. [131,135,210,211].

Respiratory and digestive systems are the most affected systems in cystic fibrosis (CF) patients [212]. In a 28-day clinical experiment, CXCR2 inhibition shows reduced neutrophils and elastase in sputum, indicating that CXCR2 antagonism may be useful for regulating respiratory disorder in CF patients [213].

To date, pharmacologic treatments, such as those using surfactants and glucocorticoids, could not improve the outcomes of ARDS. Only ventilation with lower tidal volumes could lower the mortality and reduce the number of days of ventilator use by preserving the normal ultrastructural aspect of the alveolar epithelium and reducing pulmonary edema [214–216]. Neutrophil infiltration has been considered a pathologic hallmark of this process [217,218]. Decreased neutrophils can attenuate lung vascular permeability and other indices of lung injury [219]. Blockade of CXCR2 interaction with its ligands leads to a significant reduction of migrated neutrophils into the lung [220]. In CXCR2−/− mice, PMN migration into the lung is significantly reduced in LPS-induced ALI [126,221].

5.2. Neuro-inflammatory diseases

Neuroinflammatory diseases, including multiple sclerosis (MS), traumatic brain injury (TBI) and Alzheimer's disease (AD), are associated with the interaction of chemokines with their receptors. The role of CXCR2 in the nervous system diseases is first recognized by oligodendrocyte precursor cells (OPCs) being positioned in the developing spinal cord, accompanied by CXCL1, with their migration arrested and their proliferation enhanced during the development of the nervous system [222,223]. CXCR2 is constitutively expressed in OPCs and can be upregulated in macrophages/microglia [224]. CXCR2-positive neutrophils are essential in cuprizone-induced demyelination, and CXCR2-defecient mice show significant resistance to such demyelination [225]. A significant decrease in the spinal cord white matter area and a reduction of myelin thickness are observed in CXCR2-/- mice with a reduced thickness of myelin sheaths [226]. CXCR2 can also protect OPCs from IFN-γ/CXCL10-induced apoptosis via impaired caspase 3 cleavage and elevated expression of the anti-apoptotic protein Bcl-2 [227].Inhibition of CXCR2 can decrease demyelinated lesions and increase remyelination in an experimental autoimmune encephalomyelitis (EAE) model [228]. Inhibition of CXCR2 reduces the expression of microgliosis, with astrogliosis unchanged, and shows neuroprotective effects in an Aβ1-42 induced AD model [134]. CXCR2 enhances γ-secretase activity and increases amyloid-beta (Aβ) production. Depletion of CXCR2 results in a reduction of Aβ with an increase in γ-secretase substrates [229]. CXCR2 gene polymorphism is also associated with stroke in patients with hypertension [230]. The role of neutrophils following traumatic brain injury is not clear, but CXCR2-deficient mice show reduced tissue damage and neuronal loss accompanied by unchanged blood-brain barrier permeability and functional recovery [231]. These data suggest that CXCR2 plays an essential role in the development of the nervous system and the progression of neuroinflammatory diseases.

5.3. Vascular diseases

Proinflammatory cytokines and chemokines can be detected during myocardial and cerebral ischaemia and infarction, and they recruit circulating leukocytes into the lesions and cause further damage. Additionally, leukocyte infiltration to the vascular wall is a key step in hypertension development. Neutrophils play an essential role in the development of delayed cerebral vasospasm (DCV) after aneurysmal subarachnoid haemorrhage. CSF neutrophils can be a predictive factor of DCV [232]. Anti-CXCR2 treatment significantly decreases neutrophil infiltration into the infarcted area and angiogenesis, specifically decreasing the size of the infarction area in a model of myocardial infarction. However, application of CXCL1 inhibitor shows unchanged neutrophil infiltration, which indicates that other chemokines are functioning [233]. Angiotensin II significantly upregulates the expression of CXCR2 and the number of CXCR2-positive leukocytes. The numbers of $CXCR2^+$ proinflammatory cells are also higher in hypertension patients. Inhibition of CXCR2 attenuates and even reverses the effects of angiotensin and ameliorates vascular dysfunction and aortic thickness [234].

5.4. Autoimmune diseases

ELR+ CXC chemokines attract inflammatory cells, especially CXCR2+ cells such as neutrophils, to inflammatory areas and promote the development of the disease. In a murine model of monoarticular antigen-induced arthritis, the expression levels of CXCL1, and CXCL2 are increased, and infiltration of neutrophils is obvious [100]. A further study confirmed that CXCR2 (but not another chemokine receptor) is essential for the development of autoantibody-mediated arthritis with upregulated CXCL1, CXCL2 and CXCL5 [122–124]. Although blockade of CXCLs/CXCR2 signalling seems to be a potential strategy for rheumatoid arthritis, it is necessary in osteoarthritis and pathogen-induced arthritis. A deficiency of CXCR2 decreases extracellular matrix production and increases chondrocyte apoptosis, leading to more severe osteoarthritis [235].

Infiltration of neutrophils in the skin is a characteristic of psoriasis [236]. In a murine model of imiquimod-induced psoriasis, application of CXCR2 antagonist reduces neutrophil infiltration and partly alleviates disease severity [115]. CXCR2 signalling also contributes to Sjogren's syndrome [237]. The concentrations of serum CXCL1 and CXCL8 in patients with systemic sclerosis (SSc), another kind of autoimmune disease, are higher than those in healthy individuals, patients with system lupus erythematosus (SLE) and dermatomyositis (DM).

Further, CXCL1 expression may correlate with the damage of internal organs, particularly the lung [118]. Further study confirms that CXCLs/CXCR2 signalling may not participate in the pathogenesis of inflammatory myopathies [238].

5.5. Digestive tract inflammatory diseases

Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis and is characterized by leukocyte infiltration in the bowel wall, which may cause chronic inflammation. Chemokines and their receptors are crucial in recruiting leukocytes to such tissues [239]. CXCR2, as a major receptor of CXC chemokines, is important for the pathogenesis of IBD by mediating neutrophil migration to the inflammation site [240]. To date, the CXCL8 levels have been found to be significantly elevated in the colonic mucosa of patients with IBD [141–143]. In a model of DSS-induced colitis, CXCL1 is slightly increased, and CXCR2 blockade attenuates the severity of colitis by regulating neutrophil function [106,107].

CXCR2 signalling is also involved in hepatitis and pancreatitis. The CXCL8 level is much higher in alcoholic hepatitis livers [139]. Inhibition of CXCR2 reduces neutrophil infiltration and alleviates liver injury [101]. Pathological changes in pancreatitis involves innate immunocyte migration to the pancreas. CXCR2 (-/-) mice are protected from tissue damage in acute and chronic pancreatitis. Inhibition of CXCR2 also shows the same protection and even reverses acute pancreatic inflammation [241].

5.6. Nociception (pain control)

The upregulation of chemokines may be a potential mechanism that contributes to the development and maintenance of chronic pain [242]. Nearly 50 kinds of GPCRs are involved in pain modulation [243], and CXCR2 signalling plays a role in both peripheral inflammation and nerve injury-induced pathological pain condition [244]. Neutrophils recruited by CXCL1/CXCR2 have been proven to take part in this pathological process. Neutrophil infiltration and CXCL1 expression are increased after an incision in the mouse hindpaw [113]. Depletion of neutrophils or CXCR2 blockade can markedly reduce mechanical hyperalgesia and attenuate inflammatory hypernociception [113,245–247]. In a chronic constriction injury model, CXCR2 expression is enhanced. Inhibition of CXCR2 can significantly reverse the hyperexcitability of dorsal root ganglion neurons and alleviate pain [248]. CXCR2 ligand CXCL1 is also increased in complete Freund's adjuvant-induced inflammatory pain. Application of CXCR2 siRNA can attenuate mechanical allodynia and heat hyperalgesia for more than 5 days [249].

6. The importance of CXCLs/CXCR2 axis in other pathogenic processes

CXCLs/CXCR2 signalling recruits uncontrolled leukocytes into inflammatory sites, especially in chronic inflammation and cancer. However, under certain circumstances, migration of leukocytes via CXCLs/CXCR2 signalling is essential for the recovery and homeostasis of the body.

6.1. Wound healing

CXCL1, CXCL5, CXCL8 and CXCR2 are constitutively expressed in normal human epidermis and are upregulated during wound healing processes such as epithelialization and angiogenesis. CXCR2 signalling is essential for neutrophil recruitment during wound healing [250,251]. CXCR2 knock-out mice show defective neutrophil recruitment, impaired angiogenesis and delayed cutaneous wound healing. Interestingly, the CXCR2 deficiency results in retarded wound closure, and this process can be neutrophil-independent [252]. Treatment with a CXCR2 antagonist also significantly delays wound healing in CXCR2 (+/+) mice to an even greater extent than treatment with glucocorticoids does [253].

6.2. Senescence

Cells undergoing senescence experience irreversible growth arrest and lose proliferative potential [254]. Yang et al. have found that CXCL1 can promote normal ovarian fibroblast entrance to senescence [255]. Further evidence indicates that cells undergoing OIS (oncogene-induced senescence) produce multiple CXCR2-binding chemokines, such as CXCL1, CXCL5 and CXCL8, and coordinately upregulate CXCR2 expression. CXCR2 knockout can reduce oncogene-induced senescence and DNA damage response. Ectopic expression of CXCR2 leads to premature senescence via the p53 pathway. Importantly, CXCR2 expression is increased in preneoplastic lesions and then decreases when the disease develops to advanced cancer [198]. Therefore, CXCR2 and its ligands may increase cellular senescence in early tumourigenesis as self-defence. After the disease progresses to a malignant state, CXCR2 signalling loses its ability to enhance cell growth arrest and creates a more favourable circumstances for tumour growth and metastasis [256].

6.3. Infection and sepsis

Neutrophils are known to be the fighters of infection, and migration to infection sites is one of the most important characteristics of the innate immune response to control pathogen invasion [257]. Failure to control pathogens results in their spread to blood and the development of sepsis [258]. This process is associated with CXCR2 downregulation and a failure of neutrophil migration to the infection site, although high levels of chemoattractants are still available [258,259]. Neutrophils isolated from septic patients show reduced CXCR2 expression with suppressed CXCL1, CXCL2 and CXCL5 [260]. Activation of Toll-like receptors (TLRs), such as TLR-2 and TLR-4, in neutrophils downregulates CXCR2 expression and impairs neutrophil migration into infectious sites. CXCR2 antagonists can significantly reduce neutrophil recruitment and increase the mortality rate in mice that have undergone caecal ligation and puncture (CLP) surgery [259,261]. As a major signal for neutrophil migration, blockade of CXCLs/CXCR2 leads to uncontrolled bacterial/fungal infection, including Pseudomonas aeruginosa [262], Nocardia asteroides [263], Aspergillus fumigatus [264], and Streptococcus pneumonia [265].

7. CXCLs/CXCR2-associated targeted therapy

7.1. Inhibition of CXCR2 ligands

Current therapeutic development of CXCLs/CXCR2 axis mainly focuses on targeting the receptor. However, blockade of CXCR2 ligands also shows promising treatment effects during preclinical experiments without severe side-effect. There are several common methods to inhibit CXCLs expression and function, such as blockade of signalling pathway, transfection with miRNA and application of neutralizing antibodies. Specific targeting strategies of inhibition of CXCLs are presented in Table 4.

In summary, small molecular inhibitors targeting signalling pathway can widely suppressing CXCLs expression and function, including PI3K/Akt, p38 MAPK and NF-KB inhibitors. Whereas different transduction pathways work in different function. For example, p38 MAPK inhibitors (SB203580 and SKF86002) reduce CXCL1-mediated neutrophil migration and transmigration, whereas have no effect on neutrophils rolling or adhesion [266]. Akt inhibitor (MK2206) can reduce the CXCL2 expression via limiting CXCL2 promoters activity, whereas inhibition of Erk has no effect on CXCL2 activation [267]. Inhibition of Mek/Erk phosphorylation can limit CXCL1-induced tumour cells proliferation [61]. Meanwhile, several miRNAs are

Table 4
CXCR2 ligands-associated targeted inhibition.

Ligands	Targeted strategies		Mechanism
CXCL1	**Small molecular inhibitor**		
	PI3K/AKT inhibitor	LY294002	Inhibition of PI3K/AKT pathway reduces CXCL1 secretion and attenuates liver fibrosis; Compared with patial inhibition of MAPK and p38 inhibitor, LY294002 can completely reverse EGF-induced CXCL1 production in ovarian cancer cells [108,268].
	NF-κB inhibitor	BAY11-7082	Administration of NF-κB inhibitor reduces A20-induced CXCL1 expression; Meanwhile, BAY11-7082 reduces NF-κB-mediated spinal cord astrocytes-produced CXCL1 and attenuates bone cancer pain; NF-κB inhibition completely prevents up-regulation of CXCL1 in caerulein-induced mouse pancreatitis [269–271].
	JAK inhibitor	Tofacitinib	Inhibition of JAK reduces CXCL1 expression and improves efficacy of allergen-specific immunotherapy for asthma [272].
	MEK inhibitor	PD98059	Inhibition of MEK activation reverses CXCL1-induced invasion and EMT in breast cancer cells; Inhibits CXCL1-induced ERK1/2 phosphorylation in epithelial ovarian cancer cells and reduces cell proliferation [61].
		U0126	This Mek1/2 kinase inhibitor significantly improves CXCL1-induced tumor radioresistance [65].
	IKK inhibitor	TPCA-1, IKK16 and Bay65-1942	Administration of IKK inhibitors decrease CXCL1 production, suppressing clonogenic growth of ovarian cancer cells [69].
	p38 MAPK inhibitors	SB203580 and SKF86002	Inhibition of p38 affects CXCL1-mediated neutrophil emigration and transmigration, whereas p38 inhibitors have no effect on neutrophils rolling or adhesion [266,273].
	LMP7 inhibitor	ONX-0914	Selectively targets LMP7 reduces CXCL1, 2, 3 expression, resulting in prevention of colitis-associated cancer [274].
	Multiple cytokine inhibitor	JTE-607	JTE-607 is a multiple cytokine inhibitor and reduces LPS-induced CXCL1 production and decreases accumulation of peribronchial neutrophils and perivascular edema [275].
	ATM kinase inhibitor	Ku55933	Inhibition of ATM kinase reverses CXCL1-conferred tumor radioresistance [65].
	Neddylation inhibitor	MLN4924	MLN4924 reduces CXCL1 production, promoting cell apoptosis and alleviating liver fibrosis [276].
	PKCζ inhibitor	MA130	MA130 inhibits activation of protein kinase PKCζ, reducing CXCL1 production which might be a potential target for COPD [277].
	JNK inhibitor	SP600125	SP600125 deceases CXCL1 expression in spinal cord and attenuates bone cancer pain in rats [278].
	P2Y12 receptors inhibitor	PSB0739	PSB0739 is a microglial P2Y12 receptors inhibitor, which reduces CXCL1 release and regulates brain tissue damage-associated inflammation [279].
	NAMPT inhibitor	FK866	FK866 is a nicotinamide phosphoribosyl transferase (NAMPT) inhibitor and can reduce CXCL1 level in atherosclerotic mice, attenuating neutrophil-mediated inflammation [280].
	Tyrosine kinase (PTK) inhibitor	PP2	PP2 significantly reduces CXCL1 level in serum pulmonary ischemia-reperfusion-induced acute lung injury and attenuates inflammation [281].
	Proteasome inhibitor	MG132	MG132 reduces CXCL1 secretion from brain endothelium in CNS injury and decreases neutrophils infiltration [282].
	EGFR inhibitor	PD153035	Recombinant CXCL1 can induce epidermal growth factor receptor (EGFR) phosphorylation. CXCL1-induced cell proliferation is also limited by inhibition of EGFR kinase activity [283].
	VEGF inhibitor	r84, bevacizumab, RAFL-2, GU81 and sunitinib	VEGF inhibitors reduce CXCL1 expression which is associated with decreased infiltration of MDSCs [284].
	Rho-kinase inhibitors	Fasudil and Y-27632	Fasudil and Y-27632 reduce formation of CXCL1 in colonic ischemia-reperfusion and attenuate inflammation [285].
	Farnesyltransferase inhibitors	Tipifarnib	Farnesyltransferase inhibitors (FTI) inhibit RET/PTC3-oncogene-induced CXCL1. (RET/PTC3 is a fusion oncoprotein expressed in the thyroid epithelium of patients afflicted with thyroid autoimmune disease and/or differentiated thyroid carcinoma) [286].
	Bcl-2 inhibitors	BL-193 and TW37	Inhibition of Bcl-2 decreases CXCL1 and CXCL8 expression and reduces chemokine-associated angiogenesis [287,288].
	P2 nucleotide receptors inhibitor	PPADS	Blockade of P2 nucleotide receptors abrogates LPS-induced neutrophils migration via inhibition of CXCL1 [289].
	Translocator protein (TSPO) agonist	Ro5-4864	Translocator protein (TSPO) agonist inhibits CXCL1 production and alleviates chronic neuropathic pain in a rat model [290].
	Antibodies		
	Anti-CXCL2 neutralizing Abs	Monoclonal Ab	Inhibition of CXCL1 Alleviates angiotensin II-induced cardiac hypertrophy [105]. Inhibition of CXCL1 alleviates UVB-induced inflammation and regulates tumorigenesis [291]. Anti-CXCL2 neutralizing antibody reduces bone marrow-derived mesenchymal cells migration to tumour, decreasing tumour size and lymph node metastasis in diffuse-type gastric cancer [292]. CXCL1 blockade makes tumour-infiltrating T cell more active [71]. Inhibition of CXCL1 shows stable analgesic effect in a bone cancer model [278]. Inhibition of CXCL1 improves outcome of acute kidney injury (AKI) [293]. Increased CXCL1 and angiogenesis are observed in adenosine-mediated lung disease and inhibition of CXCL1 significantly reduces angiogenesis [294]. CXCL1 neutralizing antibody blocks IKK activity and inhibits the proliferation of melanoma cells [68].
		Polyclonal Ab	PA1760 reduces spinal cord astrocytes-produced CXCL1 and attenuates bone cancer pain [270]. Blockade of CXCL1 significantly suppresses neutrophil accumulation in right ventricular (RV) during pulmonary embolism with 52% reduction in tissue myeloperoxidase (MPO), resulting in ameliorating RV failure [295]. Alleviates both the swelling and the histopathology of arthritis in murine model [295]. Anti-CXCL1 shows early benefit during sepsis, however overall survival is not different [296].

(*continued on next page*)

Table 4 (*continued*)

Ligands	Targeted strategies		Mechanism
	MiRNA		
	MiR-146a		Overexpression of miR146a reduces CXCL1 expression, alleviating renal fibrosis induced by AKI [297].
	MiR-181b		Overexpression of miR181b reduces CXCL1 and CXCL2 expression, reducing breast cancer metastasis [298].
	Others	**Biological properties**	
	Metformin	Hypoglycemic agents	Metformin inhibits CXCL1 secretion in esophageal squamous cell carcinoma via AMPK-DACH1-CXCL1 signaling, resulting in less MDSCs accumulation [299].
	Hange-shashin-to (HST)	Japanese medicine	Reduces CXCL1 expression in colon cancer and attenuate diarrhea induced by 5-Fluorouracil (5-FU) [300].
	Dexmedetomidine	Intravenous anesthetic agent	Dexmedetomidine can attenuate inflammation via reducing CXCL1 production [301].
	IMT504	Oligonucleotide	IMT504 decreases CXCL1 expression in diabetic mice, reversing immunodependent diabetes in mice [119].
	Hes1	Transcriptional repressor	Hes1 suppresses macrophage-produced CXCL1, attenuating the severity of inflammatory arthritis [302].
	Ciglitazone	Hypoglycemic agents	Ciglitazone reduces CXCL1 via microphthalmia-associated transcription factor (MITF) and inhibits melanoma development [303].
	Fudosteine	Mucoactive agent	Fudosteine significantly inhibits CXCL1 production in bronchoalveolar lavage fluid (BALF) of endotoxin- and antigen-induced airway inflammation and attenuates asthmatic inflammation [304].
	Reynosin	Herbal medicine	Reynosin reduces LPS-induced CXCL1 production in dose-dependent manner [305].
	Curcumin	Natural polyphenol compound	Curcumin decreases CXCL1 expression in colonrectal cancer, prostate cancer and breat cancer via inhibition of NF-KB, making cells more sensitive to chemotherapy [306–309].
	DK-139	Synthetic chalcone	DK-139 decreases CXCL1 expression via inhibit NF-κB pathway and suppresses invasion of human breast cancer cells [310].
	AGT ASO	AGT antisense oligonucleotide	Angiotensinogen(AGT)-antisense oligonucleotide (ASO) significantly reduces CXCL1 level in polycystic kidney disease and improves kidney function [311]
	Annexin A1	Ligand of Formyl peptide receptor 2	Annexin A1 decreases recruitment of myeloid cells in atherosclerotic lesion via inhibiting CXCL1,CCL5 and CCL2 [312]
	Dexamethasone	Corticosteroid	Dexamethasone reduces CXCL1 via inhibiting JNK pathway and attenuates inflammation in airway smooth muscle [313]
CXCL2	**Small molecular inhibitor**		
	AKT inhibitor	MK2206	MK2206 reduces the CXCL2 promoter activity and improves triple-negative breast cancer patient's prognosis, whereas inhibition of Erk doesn't decrease CXCL2 activation [267].
	IKK inhibitor	TPCA-1, IKK16 and Bay 65-1942	IKK inhibitors decrease CXCL2 production and suppresses clonogenic growth of ovarian cancer cells [69].
	MSK1 inhibitor	SB-747651A	SB-747651A enhances CXCL2-induced neutrophils adhesion and slows neutrophils migration [314].
	STAT3 inhibitor	S3I-201	S3I-201 abolishes CXCL2-induced neutrophils migration in vitro and reduces M1 protein-induced CXC chemokine production during acute lung inflammation [315].
	Rho-kinase inhibitor	Y-27632	Y-27632 decreases CLP-induced elevation of CXCL2 by 36% during sepsis; Meanwhile, it also abolishes CXCL2-induced Mac-1 up-regulation and formation of F-actin in neutrophils [316,317].
	Geranylgeranyltransferase inhibitor	GGTI-2133	GGTI-2133 markedly reduces CXCL2 level in pancreas and ameliorates severe acute pancreatitis [318].
	PI3K-γ inhibitor	AS252424	AS252424 reduces CXCL2 expression and attenuates campylobacter jejuni-induced colitis [319].
	NFAT inhibitor	A-285222	Nuclear factor of activated T cells (NFAT) inhibitor reduces taurocholate-induced CXCL2 increase and attenuates tissue damage during acute pancreatitis [320].
	NAMPT inhibitor	FK886	Nicotinamide phosphoribosyltransferase (NAMPT) inhibitor reduces CXCL2 production and dampens CXCL2-induced neutrophil recruitment and thereby attenuates tissue damage in myocardial infarction [321].
	NF-κB inhibitor	BAY11-7082	BAY11-7082 abolishes neuropeptide substance P-induced CXCL2 up-regulation; Activation of NF-κB is necessary for expression of CXCL2 [322,323].
	MAPK inhibitor	MG -132, PD98059, SB203580, UO126 and SN50	MAPK inhibitors significantly reduce ultrafine particulate matter-induces CXCL2 production; p38 MAPK and ERK/MAPK pathways are involved in CXCL2 production [324]
	JNK inhibitor	SP600125	Blockade of JNK inhibits CXCL2 mRNA expression and CXCL2 production and thereby inhibits neutrophil sequestration [325]
	Antibodies		
	CXCL2 neutralizing antibodies	Monoclonal Abs	CXCL2/CXCR2 signaling enhances intrahepatic engraftment of CXCR2-expressing colorectal cancer cells after liver resection. Anti-CXCL2 significantly delays extrahepatic tumor cell engraftment but not the growth of established metastases in patients undergoing liver resection [326]. Blocking CXCL2 reduces during hepatotoxin-mediated liver injury hepatocyte apoptosis [327].

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Table 4 (*continued*)

Ligands	Targeted strategies		Mechanism
		Polyclonal Abs	Anti-CXCL2 contributes to inhibition of neutrophils and lung edema and therefore reduces peritonitis-associated mortality [328].
	MiRNA		
	MiR-532-5p		MiR-532-5p inhibits cell proliferation and metastasis of HCC cells via inhibition CXCL2 [74].
	Others	**Biological properties**	
	Antithrombin III	Small protein molecule	Antithrombin III significantly inhibits CXCL2 level in plasma and attenuates concanavalin A (Con A)-induced liver injury [329].
CXCL3	**Small molecular inhibitor**		
	MSK1 inhibitor	H89	MSK1 is a kinase acting downstream of MEK1/2-ERK1/2. H89 inhibits CXCL3 expression in farnesol-treated lung carcinoma cells [330].
	MiRNA		
	MiR-155		Inhibition of miR-155 significantly decreases CXCL3 expression, as well as affects other inflammatory molecules, and promotes functional recovery after mouse experimental stroke [331].
CXCL5	**Small molecular inhibitor**		
	NFAT inhibitor	A-285222	A-285222 can efficiently reduce CXCL5 expression in plasma induced by cecal ligation and puncture (CLP) and regulates sepsis-associated inflammation [332].
	PI3K inhibitor	LY294002	LY294002 inhibits CXCL5/CXCR2-dependent phosphorylation of AKT and GSK-3β and thereby reduces expression of Snail/Twist, limiting tumor cells invasion and metastasis [333].
	S1PR inhibitor	FTY720	Sphingosine 1-phosphate receptors (S1PR) inhibitor inhibits LPS-induced CXCL5 expression in astrocytes and microglia which might be involved in multiple sclerosis [334].
	P2X4 antagonist	PSB-12062 and BX430	P2X4 antagonist inhibits ATP-mediated induction of CXCL5 gene expression and secretion of CXCL5 by primary macrophage [335].
	Antibodies		
	CXCL5 neutralizing antibodies	Polyclonal Abs	Inhibition of CXCL5 shows decreased metastasis of 4T1 breast cancer cells and limits tumor progression via Snail enhancement and E-cadherin down-regulation [77].
	Others	**Biological properties**	
	Curcumin	Natural polyphenol compound	CXCL5 is aberrantly increased in otitis media(OM). Curcumin reduces Nontypeable Haemophilus influenzae (NTHi)-induced CXCL5 increase via direct inhibition of IKKβ phosphorylation in OM [336].
CXCL6	**Antibodies**		
	CXCL6 neutralizing antibodies	Polyclonal Abs	Anti-CXCL6 significantly inhibits cardiac progenitor cell(CPC) migration and CPC-conditioned medium angiogenic activity [337]. CXCL6 contributes to lung fibrosis and anti-CXCL6 attenuates bleomycin-induced fibrosis [338]. Inhibition of CXCL6 protects mice from collagen-induced arthritis via limiting mobilization and infiltration of neutrophils [132].
CXCL7	**Antibodies**		
	CXCL7 neutralizing antibodies	N/A	CXCL7 contributes to glomerular endothelial injury during diabetic nephropathy and thereby anti-CXCL7 treatment leads to a marked reduction of mTORC1 activity, increase of glycocalyx, and recovery of glomerular endothelium function [133].
CXCL8	**Small molecular inhibitor**		
	NF-κB inhibitor	BAY11-7082 and SN50	NF-κB inhibitor reduces A20-induced CXCL8 expression; combination with bortezomib significantly reduces CXCL8 level and tumors growth; Also attenuates secretion of CXCL8 induced by 27-hydroxycholesterol; Decreased NF-κB activity inhibits CXCL8 expression and enhances GA and 17-AAG toxicity in castrate-resistant prostate cancer (CRPC) via increased apoptosis and necrosis (Heat-shock protein 90 inhibitor (geldanamycin (GA) and 17-allylamino-demethoxygeldanamycin (17-AAG)) [269,339–341].
	IKK inhibitor	TPCA-1, IKK16 and Bay65-1942	IKK inhibitor decreases CXCL8 production and suppresses clonogenic growth of ovarian cancer cells [69].
	Raf kinases inhibitor	Sorafenib	Sorafenib decreases CXCL8 expression in melanoma cells and inhibits cell growth and angiogenesis [89].
	Bcl-2 inhibitor	BL-193,TW37	Inhibition of Bcl-2 reduces CXCL1 and CXCL8 expression and reduces chemokine-associated angiogenesis [287,288].
	ROCK2 inhibitor	Y-27632	ROCK2 (Rho-associated, coiled-coil containing protein kinase 2) inhibitor attenuates oxidatively modified low-density lipoprotein (OxLDL)-induced NF-κB activation and CXCL8 production [342].
	ERK1/2 inhibitor	PD98059	Inhibition of ERK1/2 signal pathway significantly reduces leukemic cell lines proliferation via inducing G0/G1 cell cycle arrest and apoptosis [88].
	AMPK activator	AICAR	Activation of AMPK inhibits CXCL8 secretion from thyroid cancer cell lines and decrease migration of cancer cells [343].
	mTOR inhibitor	Rapamycin and temsirolimus	mTOR inhibitor inhibits phosphorylation of p38, ERK1/2 and NF-κB p65 and thereby attenuates expression of CXCL8 and prevents antiphospholipid antibodies-mediated thrombosis and inflammation in patients with antiphospholipid syndrome [344].
	TAK1 inhibitor	LL-Z1640-2	MAPK activation is essential for induction of CXCL8. These inhibitors reduce WNT-5B-induced CXCL8 release and attenuates pulmonary fibrosis [345]
	p38 inhibitor	BIRB0796	MAPK activation is essential for induction of CXCL8. These inhibitors reduce WNT-5B-induced CXCL8 release and attenuates pulmonary fibrosis [345].
	JNK inhibitor	SP600125	

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Table 4 (*continued*)

Ligands	Targeted strategies		Mechanism
			MAPK activation is essential for induction of CXCL8. These inhibitors reduce WNT-5B-induced CXCL8 release and attenuates pulmonary fibrosis; SP600125 shows little effect on the expression of LPS-induced CXCL8 expression in SW480 and HT-29 cell lines [345,346].
	AKT inhibitor	MK2206	MK2206 abolishes CXCL8-associated resistance of colon cancer cells to anoikis [347].
	ERK inhibitor	U0126	CXCL8 treatment enhances the resistance of CRC cells to apoptosis, whereas U0126 can limit CXCL8-associated protection effect on colon cancer cells [347].
	p38 inhibitor	GW856553	GW856553 and dexamethasone synergistically reduce CXCL8 expression in patients with COPD and improve patients' response to corticosteroid therapy [348].
		SB203580	SB203580 significantly reduces LPS-induced CXCL8 expression in SW480 and HT-29 cell lines [346]
	PI3K inhibitor	GDC-0941	GDC-0941 is a PI3K class I specific inhibitor and decreases AML cell release of CXCL8 and results in anti-proliferation and anti-angiogenesis [344].
		Wortmannin	Inhibition of PI3K pathway results in reduced cell motility but normal chemotaxis in response to CXCL8 [349].
		3-MA	3-methyladenine(3-MA) is an inhibitor of both class I and class III PI3Ks which decreases AML cell release of CXCL8 and results in anti-proliferation and anti-angiogenesis [344].
	STAT3 inhibitor	Cycloheximide	Inhibition of STAT3 abolishes CCL15-activated CXCL8 release in in both THP-1 macrophage-like cells and HEK293 cells [350].
	RhoA, Cdc42 and Rac inhibitor	TcdB-10463	TcdB-10463(Clostridium difficile toxin B-10463) reduces LPS-induced NF-κB phosphorylation and CXCL8 synthesis in endothelial cells [351].
	Src PTK inhibitor	PP2	PP2 impairs CXCL8/CXCR2-mediated neutrophils chemotaxis [349].
		SU6656	Inhibitor of Src kinases blocks CXCL8-induced VEGFR2 phosphorylation, receptor complex formation and endothelial permeability [352].
		PP1	CXCL8-induced activation of proline-rich tyrosine kinase 2 (Pyk2), a non-receptor protein tyrosine kinase (PTK), is mediated by Src not by phosphatidylinositol 3-kinase activation. With PP1 administration, CXCL8-mediated neutrophil migration is obviously inhibited [353].
	EGFR inhibitor	AG1478	AG1478 inhibits CXCL8-induced lung cancer cells proliferation [52].
	Antibodies		
	CXCL8 neutralizing antibodies	ABX-IL8 (mAb)	ABX-IL8 has no effect on transitional cell carcinoma cell lines but can significantly reduce tumor growth in vivo via down–regulation of MMP-2 and MMP-9; ABX-IL8 also inhibits angiogenesis, tumor growth and metastasis of human melanoma [354,355]
		HuMab 10F8 (mAb)	HuMab 10F8 inhibits CXCL8 expression and effectively neutralizes CXCL8-dependent neutrophil activation and migration and attenuates palmoplantar pustulosis patients' disease; HuMab 10F8 also reduces the rash induced by EGFR inhibitors [356,357].
		Humax IL8 (mAb)	Humax IL8 reduces PMN-MDSCs infiltration and enhances susceptibility to immunotherapy in triple-negative breast cancer (TNBC) [358].
	MiRNA		
	MiR-146a		Overexpression of miR-146a reduces CXCL8 expression, alleviating renal fibrosis induced by AKI [297].
	MiR-708		Transfected with miR-708 inhibits of expression of CCL11, CXCL10, CCL2 and CXCL8 [359].
	MiR-140-3p		Cells transfected with miR-140-3p show inhibition of expression of CCL11, CXCL12, CXCL10, CCL5 and CXCL8 [359].
	Others	**Biological properties**	
	IFN-γ	Dimeric soluble cytokine	IFN-γ can inhibit CXCL8-induced proliferation and migration of pancreatic cancer (PC) cells with enhancing apoptosis [360].
	Bisphenol A (BPA)	Environmental endocrine-disrupting organic chemical	BPA significantly inhibits CXCL8 expression in decidual stromal cells (DSCs), which hinders trophoblastic invasion and is associated with the rate of implantation failure of in vitro fertilization [361].
	Piperine	Herbal medicine	Piperine dose-dependently suppresses LPS-induced secretion of CXCL8 via p38 signaling other than NF-κB pathway [346].
	NSAIDs	Non-steroidal anti-inflammatory drugs	NSAIDs (naproxen, ibuprofen and oxaprozin) don't affect neutrophil degranulation, but inhibit neutrophil migration and polymerization of F-actin, in response to CXCL8, via PI3K/AKT pathway [362].
	TSG-6	Secreted glycoprotein	TNF-stimulated gene/protein-6 (TSG-6) has been identified as a CXCL8-binding protein and inhibits neutrophils migration via interaction with CXCL8 [363].
	Luteolin	Natural flavone	CXCL8 gene expression is significantly increased in vitiligo compared with control skin, and luteolin can inhibits CXCL8 release [364].
	S1P	Serum-borne bioactive lipid	T cells produce a number of cytokines and chemokines upon stimulation with TLR agonists whereas Sphingosine-1-phosphate (SlP) can suppresses CXCL8 secretion from TLR-activated T cells [365].
	Estradiol	Estrogen steroid hormone	Treatment of human peripheral monocytes with estradiol before administration of LPS reduces CXCL8 expression through an estrogen receptor-dependent mechanism [366].

Table 5
Combination strategies for anti-CXCLs/CXCR2 therapies in cancer.

Drugs	Condition	Mechanism
Anti-VEGF	Pancreatic cancer	In bevacizumab-resistance pancreatic cancer murine model, CXC receptor expresses at higher level. Following administration of a novel recombinant antibody targeting CXCR1/2 ligands, Bevacizumab-resistance cell lines show higher expression of E-cadherin and lower levels of vimentin with significantly lower myeloid cells infiltration. Inhibition of CXCR2 reduces resistance to anti-angiogenic therapy and decreases tumor burden [374].
	Ovarian cancer	Compared with responsive tumors, tumors with progression following sorafenib treatment, proangiogenic CXC chemokines and their receptors are significantly elevated. Combination of CXCR2 inhibitor with sorafenib synergistically inhibits tumour cell growth and further stabilizes tumor progression following sorafenib in vivo [375].
Anti-EGFR	Ovarian cancer	CXCL1-induced cell proliferation not only depends on CXCR2 activation but also on epidermal growth factor receptor (EGFR) phosphorylation. Combination of CXCR2 inhibitor with inhibition of EGFR kinase activity can synergistically attenuate ovarian cancer (EOC) cell lines growth [283].
	Non-small cell lung cancer	CXCL8 and both receptor CXCR1 and CXCR2 are increased in human lung cancer. CXCL8 stimulates cancer cells proliferation in a dose-dependent manner via epidermal growth factor receptor transactivation. Combination therapy can reduce CXCL8-induced cell proliferation via regulating metalloproteinase activity [52].
Anti-PD-1	Renal cell carcinoma Pancreatic ductal adenocarcinoma	CXCR2+ PMN-MDSCs are important in reducing activity of anti-PD1 antibody, and thereby simultaneously applying anti-CXCR2 and anti-PD1 therapy reduces tumor weight and enhances CD4+ and CD8+ T-cell infiltration and significantly extends overall survival [203,376].
PI3K inhibitor	Metastatic breast cancer	Metastatic cells selectively express CXCR2, not CXCR1, selectively inhibiting CXCR2 suppresses proliferation of metastatic cells but increases MIP-2 secretion via PI3K pathway, leading to resistance to CXCR2 targeted therapy [377].
Proteasome inhibition	Triple negative breast cancer	Proteasome inhibitor (bortezomib or carfilzomib) increases CXCL8 and CXCR2 expression in triple negative breast cancer which might suppress or neutralize the cytotoxic and anti-proliferative effect of proteasome inhibition. Inhibition of IKK significantly down-regulates CXCL8 activation and decreases proliferation, migration, and invasion of proteasome inhibitor-treated TNBC cells [84].
Oxaliplatin	Prostate cancer	Inhibition of CXCR2 attenuates oxaliplatin-induced NF-κB activation in metastatic prostate cancer cells and increases oxaliplatin cytotoxicity and potentiates oxaliplatin-induced apoptosis [57].
5-FU	Prostate cancer Colorectal cancer	Administration CXCR2 inhibitor increases the cytotoxicity of 5-FU by several fold in prostate cancer (CaP) cells [58]. CXCL8 is markedly increased in chemoresistance colorectal cancer cell lines. Modulation of CXCR2 pathway can regulate proliferation of chemoresistant colorectal cancer cells [86].
Paclitaxel	Breast cancer	CXCL1 is increased in paclitaxel and doxorubicin-treated mammary tumor cells which is associated chemoresistance. Inhibition of CXCR2 enhances antitumor activity of paclitaxel and meanwhile significantly inhibits of spontaneous lung metastases in vivo mammary tumor model [62].
Gemcitabine	Pancreatic ductal adenocarcinoma	Gemcitabine is commonly used for PDA treatment, but the efficacy is satisfactory. CXCL1 and CXCL8 are significantly increased in Gemcitabine-treated PDA and associated with neovascularization, which contributes to PDA chemo-resistance [71,93].

associated with CXCLs/CXCR2 axis, including miR-146a, miR-181b, miR-155, miR-708 and miR-140-3p. Among them, inhibition of miR-155 will decrease CXCLs expression, whereas the rest miRNAs decrease CXCLs expression via overexpression. Humanized monoclonal antibodies (mAbs) targeting CXCLs are not well investigated for now except for CXCL8. Two CXCL8 neutralizing antibodies, ABX-IL8 and Humax IL8, have been investigated in clinical trials. Of note, some other drugs, such as mtformin , dxamethasone and traditional herbs, can attenuates inflammation via regulation of expression of CXCLs.

7.2. Combined therapy

The pathogenesis is complicated in most diseases, especially in cancer. Blockade of CXCLs/CXCR2 axis has limited direct anti-tumour effects but regulates tumour microenvironment. Therefore, combining inhibition therapy of CXCLs/CXCR2 axis with current treatment strategies for different cancer is necessary (Table 5). Combination therapy of anti-PD1/PD-L1 and inhibition of CXCLs/CXCR2 axis for cancer is elaborated in 4.4 Immune checkpoint blockade and the CXCLs/CXCR2 axis part. Chemo- and Radio- therapy can cause inflammation and increase inflammatory factors release, including CXCLs. After chemotherapy administration, CXCLs expressions are increased and associated with response to treatment [62,367]. Decreased level of CXCL8 in serum has been identified as an indicator of response to chemotherapy and better prognosis in various cancers, especially in advanced cancer, such as metastatic melanoma [368] and stage II/IV non-small cell lung cancer [369]. In patients with esophageal cancer treated with neoadjuvant chemoradiotherapy, down-regulated CXCL8 level in tumor tissue is significantly associated with better pathological response with inactivation of NF-KB pathway [370]. Enhanced activation of CXCLs/CXCR2 axis contributes to increased MDSCs infiltration which results in tumour immune evasion and disease progression. Therefore, inhibition of CXCLs/CXCR2 axis is a promising immune regulator in anti-tumour therapies.

7.3. Inhibiting CXCLs/CXCR2 in clinical trials

The efficacy of inhibition of CXCR2 has been widely investigated in preclinical experiments. Current inhibitors of CXCR is well discussed in a former review by Helen Ha et al [371]. Therefore, we listed current clinical trials on CXCLs/CXCR2 axis in Table 6. CXCR2 antagonists have been initially considered administrated in respiratory diseases and gradually in cancer for more insights into tumour microenvironment. AZD5069 is an oral selective CXCR2 antagonist with rapid absorption rate and no severe adverse effects during phase I clinical trials (NCT00953888, NCT01051505, NCT01083238, NCT01100047, NCT01332903, NCT01480739, NCT01735240, NCT01989520). According to completed phase II trials, AZD5069 markedly reduced neutrophils in sputum and lung tissue of asthma and bronchiectasis patients. However, treatment with this inhibitor didn't improve clinical outcomes of those patients (NCT01704495, NCT01255592). The results might bring into the question the role of CXCR2-mediated neutrophils in the pathogenesis of asthma and bronchiectasis. Recently, this selective CXCR2 antagonist has shown satisfactory safety and tolerability in patients with COPD and advanced malignancies.

Reparixin is a non-competitive CXCR1/2 antagonists. It has shown promising effects on type I diabetes mellitus patients receiving islet transplantation [372]. In a phase Ib trial for HER-2-negative metastatic breast cancer, administrating combination of paclitaxel and Reparixin appeared to be safe and tolerable (NCT02001974). Its safety has also been investigated in organ transplantation (i.e., kidney, liver, lung and islet) and coronary artery bypass grafting [373]. Reparixin is a CXCR1/

Table 6
Overview of major CXCLs/CXCR2 inhibitors in clinical trials [378].

Drug name	Target	Type	Indications	Last reported Status		NCT number	Company
AZD5069	CXCR2	Small molecular inhibitor	Asthma	Phase 2	Completed	NCT01704495	AstraZeneca
			COPD	Phase 2	Completed	NCT01233232	
			Bronchiectasis	Phase 2	Completed	NCT01255592	
			Metastatic castration resistant prostate cancer	Phase 2	Not yet recruiting	NCT03177187	
			Advanced solid tumours & metastatic squamous cell carcinoma of the head and neck	Phase 1/2	Recruiting	NCT02499328	
			Metastatic pancreatic ductal adenocarcinoma	Phase 1/2	Active, not recruiting	NCT02583477	
Reparixin	CXCR1/2	Small molecular inhibitor	Pancreatectomy for Chronic Pancreatitis	Phase 3	Completed	NCT01967888	Dompé Farmaceutici S.p.A
			Islet Transplantation in Diabetes Mellitus Type 1	Phase 3	Completed	NCT01817959	
			Metastatic Breast Cancer	Phase 2	Active not recruiting	NCT02370238	
			Ischemia-reperfusion Injury in Liver Transplant/Early Allograft Dysfunction	Phase 2	Completed	NCT03031470	
			Breast Cancer	Phase 2	Terminated	NCT01861054	
			Metastatic Breast Cancer	Phase 1	Completed	NCT02001974	
			Lung Transplantation	Phase 2	Completed	NCT00224406	
			Kidney Transplantation	Phase 2	Completed	NCT00248040	
Danirixin (GSK1325756)	CXCR2	Small molecular inhibitor	COPD	Phase 2	Completed	NCT02130193	GlaxoSmithKline
			Respiratory infections	Phase 1	Completed	NCT02201303	
			Virus diseases	Phase 2	Terminated	NCT02469298	
Navarixin (SCH 527123, MK-7123)	CXCR1/2	Small molecular inhibitor	COPD	Phase 2	Terminated	NCT01006616	Merck Sharp & Dohme Corp.
			Non-small cell lung cancer Castration resistant prostate cancer Microsatellite stable colorectal cancer	Phase 2	Not yet recruiting	NCT03473925	
			Psoriasis	Phase 2	Completed	NCT00684593	
			Asthma	Phase 2	Completed	NCT00688467	
DF2156A	CXCR2	Small molecular inhibitor	Bullous pemphigoid	Phase 2	Terminated	NCT01571895	Dompé Farmaceutici S.p.A
SB-656933	CXCR2	Small molecular inhibitor	COPD	Phase 1	Completed	NCT00504439	GlaxoSmithKline
			Colitis, ulcerative	Phase 2	Terminated	NCT00748410	
			Cystic fibrosis	Phase 2	Completed	NCT00903201	
SX-682	CXCR1/2	Small molecular inhibitor	Melanoma stage III &melanoma stage IV	Phase 1	Not yet recruiting	NCT03161431	Syntrix Biosystems, Inc.
Humax IL8	CXCL8	mAb	Solid Tumor	Phase 1	Complete	NCT02536469	National Cancer Institute, Bethesda, Maryland, United States
ABX-IL8	CXCL8	mAb	COPD	Phase 2	Complete	NCT00035828	Abgenix, Fremont, California, United States

2 antagonist aiming to attenuate inflammatory reaction after organ transplantation and reduce tissue damage. It is also under investigation on breast cancer.

Danirixin, another oral selective CXCR2 antagonist, has been investigated in patients with virus infection disease (influenza). However, emergence of severe adverse events (cardiac failure and respiratory disease) in high-dose of Danirixin group leaded to termination of this small-sample clinical trial (NCT02469298). CXCR2-mediated neutrophils play an important role in anti-infection and control pathogen invasion, as we discussed above, especially in early stage of infection. Therefore, whether and when using CXCR2 antagonist as a treatment for infection-related inflammation remains unclear.

SB-656933, produced by GlaxoSmithKline, was well-tolerated in patients with cystic fibrosis. A daily dose of 50 mg could improve inflammatory markers in patients' sputum. Overall clinical outcomes need to be further investigated (NCT00903201). Meanwhile, the trial of this drug on ulcerative colitis was terminated due to no clinical benefit compared to placebo (NCT00748410).

Navarixin (Merck Sharp & Dohme Corp) has been investigated in patients with COPD and shown improved clinical outcomes. Compared to placebo group, FEV1 of Navarixin 50 mg group was significantly impoved (NCT01006616). This trial was terminated because of low enrollment. Meanwhile its safety and tolerability were verified in patients with psoriasis and asthma. Navarixin has also been investigated in cancers and data is not available.

Based on the theory of block MDSC from migrating into tumour microenvironment, SX-682, produced by Massachusettes General Hospital Cancer Center, has been investigated in stage III/IV melanoma in combination with Pembrolizumab (PD-1 inhibitor).

There are only two humanized antibodies of CXCL8 tested in clinical trials. Humax IL8 is a high-affinity, fully human, clinical-stage monoclonal anti–CXCL8 antibody. It can significantly reduce PMN-MDSCs migration into breast cancer and make tumour cells more sensitive to NK and antigen-specific T cells treatment[Neutralization of IL-8 decreases tumor PMN-MDSCs and reduces mesenchymalization of claudin-low triple-negative breast cancer]. Humax IL8 is now in phase I clinical trials for treatment of solid tumour with safety and tolerability identified(NCT02536469). ABX-IL8 is another CXCL8 neutralizing antibody which is investigated in phase II clinical trial for treatment of COPD (NCT00035828).

In summary, CXCR2 antagonist has shown promising effects on COPD treatment. Whereas, the role it plays in anti-cancer therapy needs more data to support. As we mentioned in former section, blockade of CXCR2-mediated neutrophils in infectious diseases is a double-edged sword, which emphasizes that identification the role of neutrophils during different stage of infection is important. Meanwhile, the treatment effects of CXCR2 inhibitor on asthma, bronchiectasis and ulcerative colitis are not satisfactory according to the data available.

8. Conclusion

The CXCLs/CXCR2 axis is well accepted to be a crucial chemotactic factor in various inflammatory diseases and cancer for the recruitment of immune suppressive myeloid cells from bone marrow or peripheral blood to lesions. Blockade of CXCR2 or corresponding ligands has shown benefits for prognosis in different disease models. Therefore, CXCLs/CXCR2 inhibition has been considered a promising anti-inflammatory or anti-tumour treatment. Though the outcomes of clinical trials on asthma and bronchiectasis are not satisfying, CXCR2 antagonists have shown promising effects on patients with COPD. Preclinical experiments have identified inhibition of CXCLs/CXCR2 as promising therapeutic strategy for either controlling tumour progression and metastasis or enhancing ICB efficacy. Meanwhile, based on the role CXCR2 and its ligands plays on CSCs, inhibition of CXCR2 is assumed to be a potential target on preventing cancer metastasis. What is notable is that activation of CXCLs/CXCR2 axis is essential in certain cases, such as wound healing, infection and sepsis. Therefore, the application of CXCLs/CXCR2 inhibitors or stimulators requires careful consideration. To maintain homeostasis of the human body, determining an optimal dose is also of great importance. A better understanding of the mechanism of myeloid cells function during different conditions is crucial for choosing the optimal therapeutic strategies for specific diseases.

Declaration of interest

None.

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