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CXCL2: a key player in the tumor microenvironment and inflammatory diseases

Yuanhao Lv^{1,2}, Caizheng Chen¹, Miaomiao Han¹, Chenfei Tian¹, Fuyang Song¹, Sijia Feng³, Miaoming Xu¹, Ziyin Zhao¹, Hongyan Zhou⁴, Wei Su^{2,5*} and Jiateng Zhong^{1,2,4,5,6*}

Abstract

CXCL2 (C-X-C Motif Chemokine Ligand 2), a constituent of the C-X-C chemokine subfamily, serves as a powerful chemotactic factor for neutrophils, facilitating leukocyte recruitment and movement while initiating an inflammatory response. Recent investigations have demonstrated the pivotal involvement of CXCL2 in carcinogenesis. Within the tumor microenvironment, CXCL2 modulates cellular activity primarily via its interaction with the CXCR2 receptor. The activation of signaling pathways, including ERK/MAPK, NF- κ B/MAPK, PI3K/AKT, and JAK/STAT3, highlights CXCL2's inclination to promote tumorigenesis. Furthermore, the role of CXCL2 encompasses inflammatory conditions like lung inflammation, atherosclerosis, and obesity. This article examines the structural characteristics, biological roles, and molecular foundation of CXCL2 in carcinogenesis and inflammatory disorders.

Keywords Chemokine, CXCL2, Tumor microenvironment, Inflammatory diseases, Targeted therapies

Introduction

The tumor microenvironment (TME) is a complex ecosystem comprising cancer cells, immune cells, fibroblasts, and the extracellular matrix (ECM). This intricate network fosters chronic inflammation, immunosuppression, and angiogenesis, thereby supporting cancer progression

and metastasis [1]. Within this environment, cancer cells interact with stromal components to evade immune surveillance and promote their survival and proliferation [2]. Understanding the TME has become crucial for identifying novel therapeutic targets, with the chemokine system emerging as a key player in cancer immunotherapy [3].

Chemokines are small cytokines that regulate immune cell migration and activation. They are classified into four subfamilies: CXC, CC, C, and CX3C, based on their structural motifs [4]. Among these, the CXC chemokines, particularly those containing the ELR motif (e.g., CXCL1, CXCL2, and CXCL8), are known for their roles in neutrophil recruitment, angiogenesis, and cancer progression [5]. CXCL2, also known as macrophage inflammatory protein 2 α (MIP2- α) or growth-regulated oncogene β (GRO- β), is a prototypical ELR + CXC chemokine that drives neutrophil migration and activation [6]. It is predominantly produced by monocytes, macrophages, and endothelial cells in response to inflammatory stimuli such as TNF α , IL-1 β , and LPS [7].

*Correspondence:

Wei Su

hnswei@163.com

Jiateng Zhong

jtzhang@xxmu.edu.cn

¹Department of Pathology, Xinxiang Medical University, Xinxiang, China

²Department of Pathology, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China

³Department of Pathology, The Third Affiliated Hospital of Xinxiang Medical University, Xinxiang, China

⁴Xinxiang Key Laboratory of Precision Diagnosis and Treatment for Colorectal Cancer, Xinxiang First People's Hospital, Xinxiang, China

⁵Xinxiang Engineering Technology Research Center of Digestive Tumor Molecular Diagnosis, Xinxiang Medical University, Xinxiang, China

⁶Henan Province Engineering Technology Research Center of Tumor diagnostic biomarkers and RNA interference drugs, The Third Affiliated Hospital of Xinxiang Medical University, Xinxiang, China



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Recent studies have highlighted the pivotal role of CXCL2 in both cancer and inflammatory diseases. Within the TME, CXCL2 interacts with its receptor CXCR2 to modulate signaling pathways such as ERK/MAPK, NF- κ B, PI3K/AKT, and JAK/STAT3, thereby promoting tumorigenesis, metastasis, and immune evasion [8]. Additionally, CXCL2 is implicated in various inflammatory conditions, including lung inflammation, atherosclerosis, and obesity, where it drives neutrophil recruitment and exacerbates chronic inflammation [9–11]. This review aims to provide a comprehensive overview of the structural characteristics, biological functions, and molecular mechanisms of CXCL2 in cancer and inflammatory diseases, highlighting its potential as a therapeutic target.

CXCL2 and its receptor CXCR2

CXCL2 is a key member of the ELR+CXC chemokine subfamily, characterized by its potent neutrophil chemoattractant properties. First identified in 1988 alongside CXCL1 and CXCL3, CXCL2 is encoded on chromosome 4q21 and shares significant sequence homology with other ELR+ chemokines [12, 13]. Structurally, CXCL2 is synthesized as an inactive precursor protein (107 amino acids) and is activated through proteolytic cleavage to its mature form (amino acids 5–73) by membrane-type 6 matrix metalloproteinase [14, 15]. This active form binds specifically to CXCR2, a G protein-coupled receptor, to mediate its biological effects [8]. Figure 1 visualizes the unique structure of CXCL2.

Regulation and function of CXCL2

CXCL2 expression is tightly regulated by various inflammatory stimuli, including TNF α , IL-1 β , and LPS, which

induce its production through NF- κ B and MAPK signaling pathways [7, 16]. As a critical mediator of neutrophil migration, CXCL2 facilitates the recruitment of neutrophils across the endothelium, a process essential for effective immune responses and tissue repair [17]. Beyond its role in immunity, CXCL2 is involved in multiple biological processes, including angiogenesis and wound healing [8].

CXCR2: receptor dynamics

CXCR2, identified in 1991, is a key receptor for ELR+CXC chemokines and is predominantly expressed on neutrophils, endothelial cells, and monocytes [18, 19]. The CXCR2 gene, located on chromosome 2q34-q35, contains 11 exons and encodes a receptor that mediates chemotaxis and activation of immune cells [20]. Dysregulation of CXCR2 signaling has been implicated in various pathological conditions, including cancer progression and chronic inflammation. In cancer, CXCR2 overexpression correlates with poor prognosis and enhanced metastasis, highlighting its role in tumor biology, such as acute myeloid leukemia [21], invasive ductal breast cancer [22], colorectal cancer [23], esophageal cancer [24], gastric cancer [25, 26], intrahepatic cholangiocarcinoma [27], squamous cell carcinoma of the larynx [28], adenocarcinoma of the lungs [29], non-small-cell lung carcinoma [30], and ovarian carcinoma [31, 32].

Pathophysiological roles

The CXCL2-CXCR2 axis is central to neutrophil recruitment and activation, processes that are critical for host defense against infections and tissue repair. However, this pathway can also drive pathological inflammation and cancer progression. For example, in cancer,

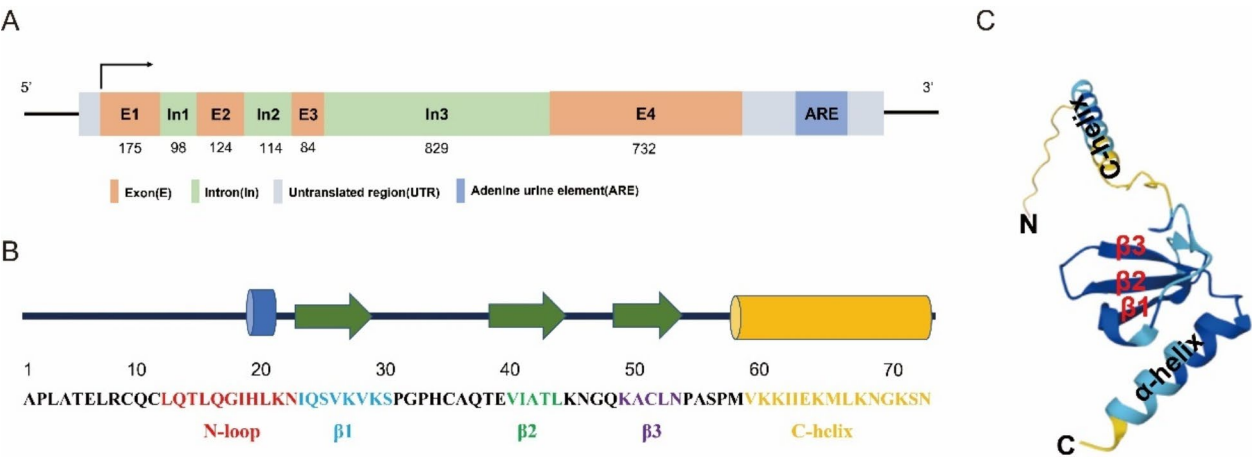


Fig. 1 CXCL2 Structure. **A** rectangular rectangle illustrates the gene structure of CXCL2, with lengths denoted in base pairs. The CXCL2 gene comprises exons, introns, untranslated regions (UTRs), and adenine-rich elements (AREs). **B**. Amino acid sequence of CXCL2. **C**. Spatial configuration of the CXCL2 monomers. The gene structure of CXCL2 was obtained from Ensembl113 [35]. The CXCL2 amino acid sequence was obtained from UniProt [36] and examined using IBS 2.0 [37]. The spatial configuration of CXCL2 was obtained from AlphaFold 3 [38]

CXCL2-CXCR2 signaling promotes tumor growth and immune evasion by enhancing the infiltration of myeloid-derived suppressor cells (MDSCs) and neutrophils into the tumor microenvironment [33, 34]. In inflammatory conditions such as atherosclerosis and obesity, CXCL2 drives neutrophil recruitment and exacerbates chronic inflammation [9, 11].

Regulation of CXCL2

Figure 2 illustrates the molecular pathways regulating CXCL2 expression. The expression of CXCL2 is meticulously controlled by several variables, including inflammation-inducing agents, oncogenes, and microRNAs (miRNAs) [12, 39]. Research indicates that IL-1 β markedly elevates CXCL1 and CXCL2 gene expression in rat pancreatic islets and β -cell lines via the NF- κ B pathway in activated B cells. The upregulation of these genes enhanced neutrophil recruitment, consequently exacerbating islet inflammation [40]. Lipopolysaccharide

activates NF- κ B and c-Jun transcription factors in macrophages through Toll-like receptor (TLR)-dependent signaling pathways. The CXCL2 gene is swiftly activated to provoke inflammation by the recruitment of neutrophils, facilitated by the synergistic interaction of NF- κ B and c-Jun transcription factors [16]. Butcher et al. discovered that the IL-17 A/IL-17RA axis exacerbates inflammation in the aortic arch and facilitates the adhesion and migration of neutrophils and monocytes during atherosclerosis by upregulating aortic CXCL2 expression [10]. Innate lymphoid cells (ILCs) are a diverse group within the innate immune system, predominantly located at mucosal surfaces, and play a crucial role in regulating immunological homeostasis. ILCs can transdifferentiate into various subpopulations through interactions with the tumor microenvironment, leading to either pro- or anti-tumor immunity [41]. Xu et al. examined the function of type II intrinsic lymphocytes (ILC2s) in hepatocellular carcinoma (HCC). ILC2s were reported to facilitate HCC

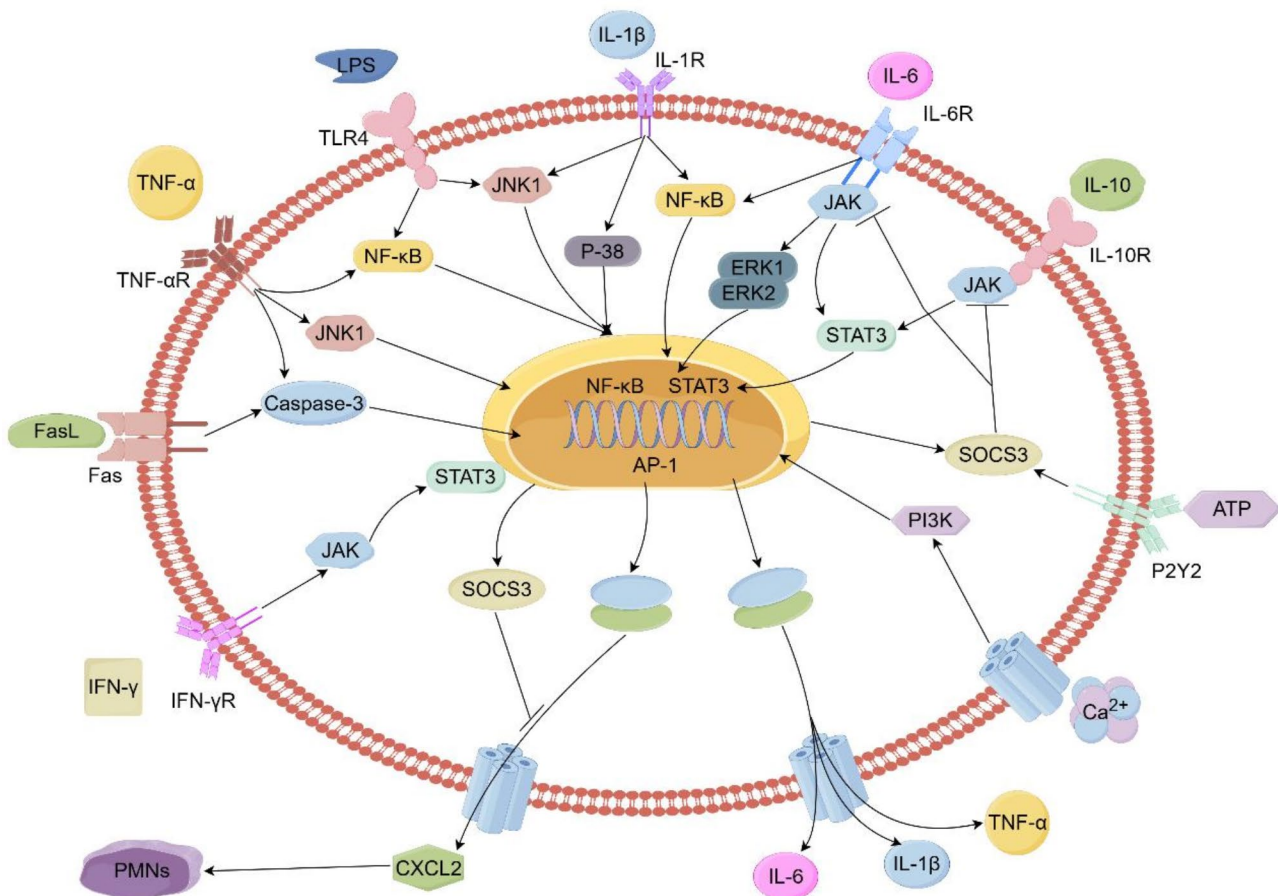


Fig. 2 Molecular processes underlying CXCL2 secretion. The illustration depicts multiple interacting molecular pathways involved in the secretion of CXCL2. The processes encompass: LPS-induced CXCL2, IL-6, IL-1 β , and TNF- α via the NF- κ B/MAPK signaling pathway; IL-6 facilitating CXCL2 induction through the NF- κ B/MAPK pathway; TNF- α promoting CXCL2 induction via both the NF- κ B/MAPK and caspase-3 pathways; FasL inducing CXCL2 through the caspase-3 pathway; Ca²⁺ and ATP stimulating CXCL2 induction through the PI3K signaling pathway; IL-1 β facilitating CXCL2 induction via the NF- κ B/MAPK pathway; and IFN- γ and IL-10 inhibiting CXCL2, IL-6, IL-1 β , and TNF- α induction through the JAK/STAT3 signaling pathway, with SOCS3 mediating JAK/STAT3 inhibition. TNF- α : tumor necrosis factor-alpha; IFN- γ : interferon-gamma; IL: interleukin; LPS: lipopolysaccharide

progression by enhancing the secretion of CXCL2 and CXCL8, thereby attracting neutrophils and establishing an immunosuppressive milieu that contributes to HCC development [42]. Recent findings indicate that KDM4C enhances the proliferation and migration of HCC cells while inhibiting their radiosensitization through the upregulation of CXCL2 expression [43]. Conversely, miR-532-5p acts as a tumor suppressor in human osteosarcoma cells by inhibiting the production of CXCL2 [39].

The role of CXCL2 in cancer

CXCL2 exhibits significant pro-oncogenic effects in a variety of cancers, including pancreatic cancer (PAAD) [44], kidney clear cell carcinoma (KIRC) [45] and stomach cancer (STAD) [46] and its up-regulation of expression in the TME is closely associated with tumor progression [47–49]. CXCL2 activates multiple signaling pathways (e.g., ERK/MAPK, PI3K/AKT, JAK/STAT3, etc [50]), through interactions with the CXCR2 receptor, which promotes the proliferation, migration and immune

escape of tumor cells. In addition, the role of CXCL2 in immune infiltration is particularly critical, especially its interaction with tumor-associated macrophages (TAMs) and neutrophils, which play an important immunomodulatory role in the tumor microenvironment. However, recent studies also highlight the potential dual roles of CXCL2 in cancer, with some evidence suggesting its involvement in tumor suppression under certain conditions [51]. Here, we summarize the functions and mechanisms of CXCL2 in the progression of five of the deadliest cancers, as detailed in Table 1, and discuss the dual roles of CXCL2, summarizing its paradoxical functions in tumor suppression and promotion.

Colorectal cancer

CXCL2 is a potential predictive biomarker for colon cancer, as its expression is heightened in colon cancer patients and corresponds with prognosis [52]. Luo et al. identified a correlation between CXCL2 and diminished overall survival (OS) in colorectal cancer through

Table 1 The function and mechanisms of CXCL2 in the advancement of tumors associated with the highest cancer-related death rates

Type of cancer	Impact on cancer	Study model	Reference
Colorectal cancer	Possible prognostic biomarker	Bioinformatic analysis of patient databases	[101]
	Promote metastasis	Mice model	[54]
	Induce cancer stem cell phenotype	In vitro	[102]
	Induce EMT and activates PI3K-Akt-NF-κB signaling	In vitro	[103]
	Promote cancer stem cell phenotype	In vitro	[104]
Lung cancer	Predicts poorer DFS and OS	Patient survival data	[64]
	Promotion of lung cancer metastasis	In vitro	[105]
	Promoting migration of MDSCs into the tumor microenvironment	In vitro	[34]
	Promotes angiogenesis, tumor development and metastasis	In vitro	[106]
	Involved in the resistance of non-small cell lung cancer cells to anlotinib	In vitro	[69]
Breast cancer	Negatively associated with staging, survival and prognosis of BC patients	Bioinformatic analysis of patient databases	[79, 107]
	Activation of ERK1/2/NF-κB/Stat3 signaling cascade	In vitro	[50]
	Candidate markers associated with chemoresistance in breast cancer	In vitro	[108]
	A basis for predicting the efficacy of 5 - FU in the treatment of breast cancer	In vitro	[51]
	Schwann cell-derived CXCL2 contributes to cancer pain by modulating macrophage infiltration in a mouse breast cancer model	Mice model	[109]
Liver cancer	Involved in fasciculation stress-induced recruitment of myeloid cells in tumor tissues	In vitro	[33]
	Promote the development and metastasis of HCC	Patients with hepatocellular carcinoma	[82]
	Widely associated with the immune microenvironment of HCC	In vitro	[110]
	Induction of lipid remodeling in hepatocellular carcinoma cell lines	In vitro	[99]
	As a biomarker and potential target in hepatocellular carcinoma	Bioinformatic analysis of patient databases	[111]
Gastric cancer	Involved in the common molecular mechanisms of obesity and GC	Bioinformatic analysis	[112]
	May serve as a prognostic biomarker for gastric adenocarcinoma and correlates with immune infiltration	Bioinformatic analysis	[90]
	Mediated the transformation of omental adipocytes triggering GC cells to an invasive phenotype, inducing angiogenesis, followed by cell growth and peritoneal metastasis	In vitro	[93]
	Plays an important role in the pathogenesis of GC and can be used as a marker for the development of GC	Gastric cancer patients	[92]

a retrospective study [53], indicating that CXCL2 may serve as a valuable prognostic marker for tumor features and survival in CRC patients. In vitro, CXCL2 activation enhances the proliferation and migration of colon cancer cells [54]. This may result from the interaction of CXCL2 with its receptor CXCR2, as the antagonism of CXCR2 diminishes metastasis in vivo. The positive link between CXCL2 and metastatic potential may also be associated with CXCL2's ability to generate cancer stem cells [55].

Moreover, CXCL2 has been demonstrated to have a substantial correlation with immune infiltration in colorectal cancer [56]. SNAIL facilitates epithelial tumor transformation, while converted mesenchymal stromal cells release CXCL2, which enhances M2-type macrophage infiltration and tumor cell metastasis. These findings clarify the relationship between tumors and tumor-associated macrophages in the metastatic microenvironment, mediated by tumor-derived CXCL2, which influences lung metastasis [57]. Tumor expansion has recently garnered significant interest in the evolution and invasion of several malignancies, including colorectal cancer (CRC). Tumor outgrowth refers to the existence of solitary tumor cells or clusters of up to four cells at the invasive front [58, 59]. High-grade tumor outgrowth has been recognized as an independent prognostic factor, correlating with reduced disease-free survival (DFS) and overall survival (OS) across various cancers [59–61]. Guil-Luna et al. identified the up-regulation of many chemokine receptors and ligands, notably CXCL2 and CXCR2, in hyperdifferentiated tumor outgrowth in colorectal cancer (CRC), indicating that CXCL2 and its receptor CXCR2 facilitate high-grade tumor outgrowth and enhance tumor invasion in CRC [62].

Lung cancer

The aberrant production of CXCL2 was markedly correlated with the clinical cancer stage in lung adenocarcinoma (LUAD) relative to normal tissues, and Wang et al. additionally discovered that immune cell infiltration was strongly linked to the CXC chemokine-mediated LUAD microenvironment [63]. Gu et al. assessed CXCL2 expression using immunohistochemical techniques in tumor tissue samples from 232 primary non-small cell lung cancer (NSCLC) patients at TNM stages I–IIIA, revealing its varied potential as a biomarker for tumor characteristics and survival in NSCLC patients [64].

CXCL2 is believed to potentially stimulate PD-L1 expression in lung adenocarcinoma cells due to interactions between cancer cells and cancer-associated fibroblasts (CAFs) [65]. Notably, alterations in CXCL2 following anti-PD-1 therapy were sustained in patients with improved clinical outcomes, including those experiencing tumor pseudoprogression. Due to the ease of measuring CXCL2 through minimally invasive blood draws,

it can be utilized to evaluate the clinical prognosis of NSCLC patients undergoing treatment with PD-1 inhibitors [66]. CXCL2 can function as a target gene for various other genes that facilitate lung cancer progression. CUL4B directly binds to the CXCL2 promoter and epigenetically inhibits its transcription. Deletion of CUL4B elevates the expression of CXCL2, which interacts with CXCR2 on MDSCs and facilitates their migration into the tumor microenvironment. Targeting MDSCs markedly postpones the proliferation of CUL4B knockdown KRAS mutant tumors [34]. microRNA-27a-3p functions as an oncogene that modulates lung macrophage proliferation and chemotaxis via CXCL2 in non-small cell lung cancer tissues [67]. A study demonstrated that NKX2-1 modulates pro-tumor neutrophil infiltration by suppressing CXCLs/CXCR2-dependent pathways and proposed that targeting CXCR2 in NKX2-1-deficient tumors could serve as a viable anti-tumor therapy, potentially enhancing the prognosis for LUAD patients [68]. Additionally, CXCL2 has a role in the resistance of lung cancer cells to anlotinib [69].

Breast cancer

There is growing evidence that CAFs contribute to chemoresistance in breast cancer therapy [70]. CAFs, as the predominant stromal cell component of the tumor microenvironment, are believed to significantly contribute to the progression of breast cancer [71, 72]. Researchers utilized cytokine arrays to identify a collection of mechanically triggered cytokines, including CXCL2, within the osteoblast secretome that may facilitate breast cancer metastasis [73]. LAMB3 expression exhibited a favorable correlation with CXCL2, and collectively they facilitated CAF invasion [74].

In the initial phases of breast cancer, malignant cells invade the adjacent adipose tissue, resulting in the activation and conversion of nearby adipocytes into cancer-associated adipocytes (CAA) [75, 76]. This confers an advantage for the survival, proliferation, and metastasis of breast cancer cells [77]. CAAs exhibit inflammatory alterations and secrete elevated levels of pro-inflammatory cytokines compared to normal adipocytes, hence facilitating breast cancer proliferation and metastasis [75, 78]. A 2022 study shown that CAA and breast cancer cells interact through the secretion of the cytokine leukemia inhibitory factor (LIF) and C-X-C subfamily chemokines (CXCLs), respectively. LIF is a proinflammatory cytokine released by CAA that facilitates the migration and invasion of breast cancer cells via the Stat3 signaling pathway. The activation of Stat3 leads tumor cells to secrete ELR motif CXCLs, specifically CXCL1, CXCL2, CXCL3, and CXCL8. Notably, CXCLs subsequently triggered the ERK1/2/NF- κ B/Stat3 signaling pathway and enhanced LIF expression in CAA [50].

Wang et al. identified CXCL2 as a potential therapeutic target for breast cancer and a biomarker for breast cancer patients, as assessed by bioinformatics methods. Furthermore, it has been linked to immunological infiltration [79]. Pan et al. formulated a novel immunotherapy for breast cancer utilizing N1-type neutrophils with anticancer capabilities to augment the cytotoxic activity of T lymphocytes against cancer cells. They amalgamated CXCL2 plasmid DNA with inactivated Sendai virus (hemagglutinating virus of Japan) envelope (HVJ-E). The amalgamation of CXCL2 DNA and HVJ-E (C/H) impeded the proliferation of murine breast cancer in a syngeneic model by enhancing the expansion of cytotoxic T-lymphocytes and mitigating lung metastasis from the initial tumor location. The delivery of anti-PD-1 antibody was shown to augment the anticancer efficacy of C/H therapy via neutrophil-mediated activation of cytotoxic T lymphocytes [80].

Liver cancer

Increased expression of the CXCL2 gene in tumor tissues throughout the evolution of hepatocellular carcinoma [81]. A study analyzed serum CXCL2 concentrations in 80 patients with hepatocellular carcinoma (HCC), 65 patients with benign liver conditions, and 60 healthy volunteers with an enzyme-linked immunosorbent test (ELISA). Serum CXCL2 concentrations in benign conditions and healthy individuals were significantly lower than in HCC and exhibited correlations with tumor-node-metastasis (TNM) stage, tumor dimensions, vascular embolism, cysts, and Edmondson classification in HCC ($P < 0.05$), but not with gender, age, cirrhosis, or AFP levels ($P > 0.05$) [82].

Moreover, the CXCL2-CXCR2 axis may provide a novel target for anti-angiogenic therapy in hepatocellular carcinoma [83]. Jiang et al. discovered that continuous constraint stress enhances the proliferation of hepatocellular carcinoma via stimulating β -adrenergic signaling and recruiting splenic myeloid cells into tumor tissues. Mechanistic investigations demonstrated that restraint stress enhanced the expression of CXCL2/CXCL3 in tumor tissues and modified CXCR2 expression in myeloid cells. Furthermore, the CXCR2 inhibitor SB225002 impeded the recruitment of myeloid cells in tumor tissues and suppressed tumor growth in stressed mice [33]. Recombinant human CXCL2 markedly increased the migration and invasion of SMMC7721 cells while diminishing adherence. Conversely, the neutralization of CXCL2 and the blockage of CXCR2 markedly diminished the impact of CXCL2 on SMMC7721 cells, indicating that CXCL2 may be pivotal in HCC metastasis [84].

Further mechanistic investigations have demonstrated that CXCL2 serves as a target for many genes that regulate the evolution of hepatocellular carcinoma.

Knockdown of KDM4C enhances the association of H3K36me3 with the CXCL2 promoter, hence elevating CXCL2 expression and facilitating CXCL2 secretion in HCC cells [43]. miR-532-5p functions as a tumor suppressor in hepatocellular carcinoma by targeting and inhibiting CXCL2 [85].

CXCL2 significantly influences the immunological microenvironment in patients with hepatocellular cancer. Peng et al. discovered that monocyte-derived CXCL2 is a primary factor governing neutrophil recruitment to the tumor microenvironment in hepatocellular cancer. Besides tumor-derived soluble substances, these chemokines prevent neutrophil death and promote their survival, resulting in neutrophil aggregation in tissues [86]. Simultaneously, the degradation of CXCL2 diminishes neutrophil recruitment to tumors and the creation of neutrophil extracellular traps, so ultimately impeding HCC progression [87]. CXCL1 and CXCL2 were identified as possible paracrine proteins secreted by M2 tumor-associated macrophages that enhance the resistance of hepatocellular carcinoma cells to sorafenib (SOR). Pharmacological inhibitors revealed that CXCR2/ERK signaling is essential for SOR resistance mediated by CXCL1 and CXCL2 [88]. Moreover, the effectiveness of lenvatinib against tumor cells is diminished due to its capacity to enhance neutrophil recruitment by prompting neutrophils to release CXCL2 and CXCL5 within the tumor microenvironment. Upon entering the tumor microenvironment, neutrophils polarize towards the N2 phenotype. Concurrently, PD-L1 expression is increased [89].

Gastric cancer

In stomach adenocarcinoma (STAD) tissues, CXCL2 levels are markedly elevated. A robust association exists between CXCL2 levels and immune cells as well as immunological biomarkers. Elevated CXCL2 expression in STAD is associated with a positive outcome. CXCL2 has been linked to resistance against multi-drug or small molecule therapies in STAD patients [90]. CXCR2 signaling significantly influences the gastric tumor microenvironment within the pathogenic framework of tumor fibroblasts, indicating that gastric cancer (GC) cells may modify adjacent stroma to establish a conducive environment for tumor advancement [91]. CXCL2 has a significant part in the etiology of gastric cancer and may function as a marker for its development [92]. Omental adipocytes cause the development of an invasive phenotype in gastric cancer cells via the production of CXCL2, which promotes angiogenesis and subsequently facilitates cell proliferation and peritoneal metastasis [93].

Furthermore, the role of CXCL2 extends beyond the aforementioned diseases to encompass pancreatic cancer [94], ovarian cancer [95], thyroid tumors [96], and glioblastoma [97].

CXCL2 and immune infiltration

CXCL2 plays a key role in immune infiltration in the TME, particularly in regulating the behavior of TAMs and neutrophils. CXCL2, through the activation of its receptor, CXCR2, is capable of significantly affecting the function of these immune cells, thereby promoting tumor progression.

TAMs exhibit immunosuppressive properties in the TME, and the extent of their infiltration is closely related to the malignancy of the tumor. CXCL2 is able to inhibit anti-tumor immune responses by activating TAMs through the CXCR2 receptor and inducing their polarization toward the M2 type. For example, in CRC, CXCL2 expression is positively correlated with M2-type macrophage infiltration, and this infiltration contributes to tumor cell metastasis and immune escape [57]. In addition, CXCL2 was able to further enhance the immunosuppressive function of TAMs by activating the PI3K/AKT and NF- κ B signaling pathways in them [98].

Neutrophils play a complex dual role in the TME, promoting tumor progression as well as participating in anti-tumor immunity. CXCL2 is one of the major chemokines for neutrophils and is able to mediate neutrophil recruitment via the CXCR2 receptor [99]. In HCC, high expression of CXCL2 is closely associated with infiltration of neutrophils, which further promote tumor progression by releasing extracellular traps (NETs) and pro-inflammatory cytokines [87]. In addition, CXCL2 was able to enhance neutrophil survival and function by activating the JAK/STAT3 signaling pathway [86].

CXCL2 not only promotes tumor progression by directly acting on immune cells, but is also able to form an immunosuppressive microenvironment by regulating the interactions between immune cells. For example, in breast cancer, CXCL2 expression forms a positive feedback loop with interleukin-6 (IL-6) secreted by CAAs, which further activates the Stat3 signaling pathway, thereby enhancing neutrophil recruitment and immunosuppression [50]. This immunosuppressive microenvironment contributes to the proliferation and metastasis of tumor cells and also reduces the efficacy of immunotherapy [100].

CXCL2 plays a multifaceted role in immune infiltration in the tumor microenvironment, and its interaction with TAMs and neutrophils is a key mechanism for tumor progression and immune escape. Future studies need to further explore the specific mechanisms of CXCL2 action in different tumor types and develop targeted therapeutic strategies against the CXCL2/CXCR2 axis to improve the prognosis of cancer patients.

Dual roles in tumor suppression and progression

While CXCL2 is predominantly associated with tumor progression, recent studies have highlighted its potential

dual roles in cancer. For example, in some contexts, CXCL2 may contribute to tumor suppression by promoting neutrophil-mediated killing of cancer cells [51]. This dual functionality underscores the complexity of CXCL2's role in cancer biology and highlights the need for a nuanced understanding of its mechanisms. The conflicting evidence suggests that CXCL2's effects may vary depending on the tumor type, stage, and microenvironmental context, emphasizing the importance of further research to elucidate its precise roles.

In conclusion, CXCL2 plays a significant role in various cancers by promoting tumor cell proliferation, migration, and metastasis through its receptor CXCR2 and downstream signaling pathways such as ERK/MAPK, PI3K/AKT, and JAK2/STAT3. Its upregulation is associated with poor prognosis in colorectal, lung, breast, liver, and gastric cancers. These findings highlight CXCL2 as a potential prognostic biomarker and therapeutic target, warranting further investigation into its molecular mechanisms and targeted interventions.

The role of CXCL2 in inflammatory diseases

Inflammation is the body's initial response to infections, irritants, or injury [113]. CXCL2 is crucial for recruiting inflammatory cells, and its transcription is regulated by heterodimeric chaperones, influencing neutrophil recruitment [114]. CXCL2 contributes to inflammatory diseases such as lung inflammation, atherosclerosis, and obesity (Fig. 3).

Lung inflammation

Efficient host defense against pulmonary bacterial infections predominantly depends on the swift elimination of the pathogen from the respiratory tract. Initial bacterial clearance is facilitated by a dual phagocytic mechanism involving neutrophils (PMNL) and macrophages [115]. The recruitment and activation of inflammatory cells at the infection site necessitate the synchronized expression of leukocytes and vascular adhesion molecules, alongside the formation of a chemotactic gradient via chemotaxis and cytokine production activation. CXCL2 can induce several types of pneumonia by chemotaxis. Preliminary research indicates that CXCL2 serves as a significant mediator in the recruitment of pulmonary PMNLs and the clearance of *Klebsiella pneumoniae* [116]. Fitch et al. similarly discovered that following infection with *Chlamydia pneumoniae*, there was an increase in CXCL2 release, which attracted neutrophils and lymphocytes, correlating with the creation of ectopic lymphoid tissue [117].

Chronic obstructive pulmonary disease (COPD) exemplifies the lung inflammations linked to CXCL2. COPD is defined as a "condition marked by airflow restriction that is not completely reversible" [118]. Recent investigations

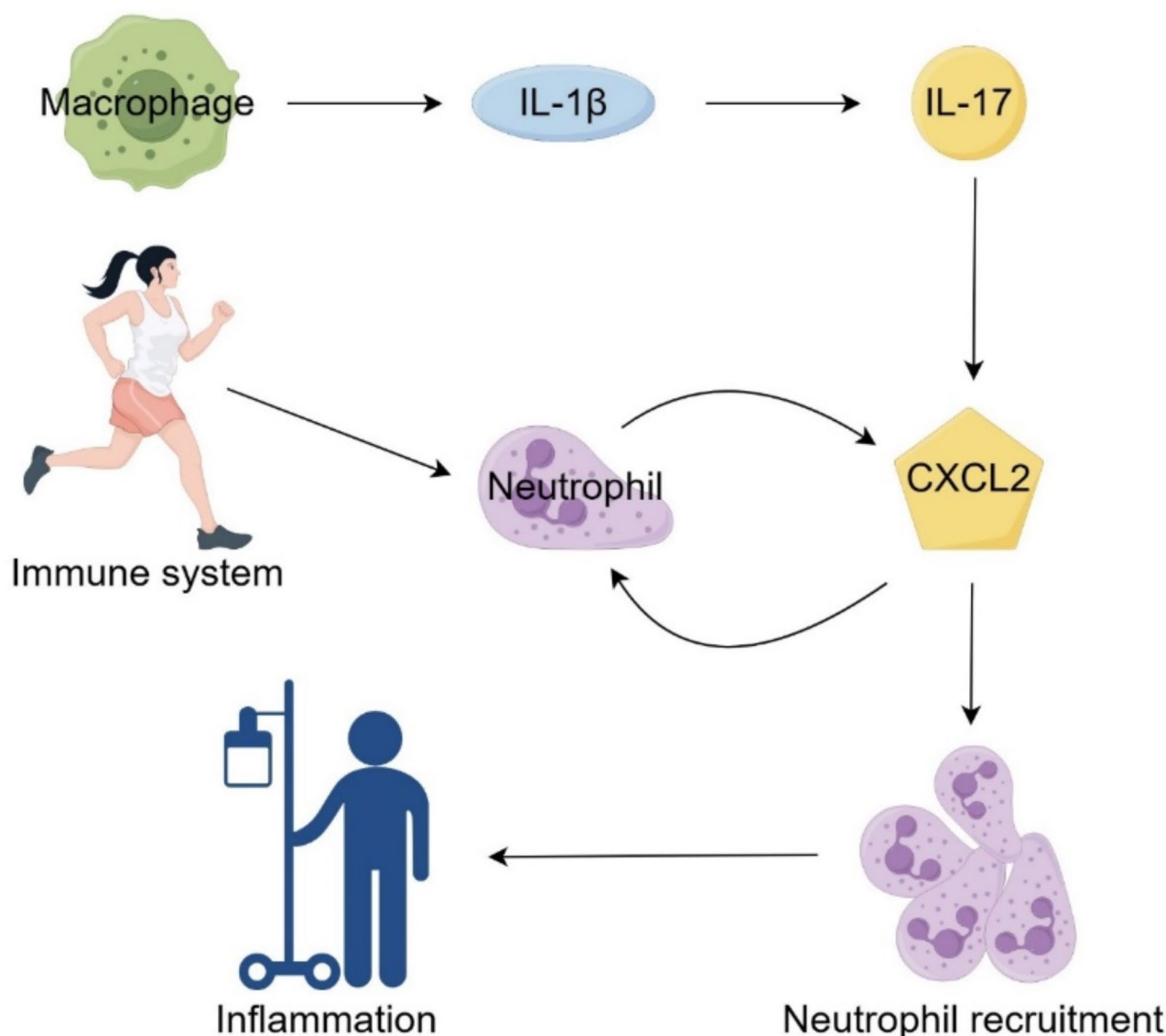


Fig. 3 The expression and primary function of CXCL2 in the context of inflammation. In the course of inflammation, neutrophils release chemokines such as CXCL2, which also provides negative feedback to neutrophils. Neutrophils drive CXCL2 expression not just through autocrine mechanisms but also via CXCL1, whereas mast cells similarly promote CXCL2 expression. Macrophages stimulate the production of the cytokine interleukin-1 β (IL-1 β), which subsequently enhances the T cell-derived cytokine IL-17, leading to the upregulation of the chemokine CXCL2 that facilitates neutrophil recruitment during inflammation. Consequently, CXCL2 influences neutrophils to enhance their recruitment and adherence, thereby facilitating inflammation

indicate that medicines can suppress airway inflammatory responses in mice models of COPD and in people by diminishing CXCL2 secretion [119–121]. Given the significant function of CXCL2 in lung inflammation, it may serve as a potential therapeutic target.

Osteoarthritis

CXCL2 is intricately linked to many forms of arthritis as a chemokine primarily produced by neutrophils, facilitating the recruitment and migration of immune cells. This chemokine is crucial for the proper rupture of endothelial junctions, enabling neutrophils to traverse the venous

wall [17]. In rheumatoid arthritis (RA), CXCL2 facilitates the migration of CD14⁺ monocytes in patients and induces osteoclast formation via the ERK, MAPK, and NF κ B pathways [122]. The significance of CXCL2 in psoriatic arthritis [123] and septic arthritis [124] has been examined in numerous research.

Atherosclerosis

Atherosclerosis is a prevalent cardiovascular condition [125]. Research indicates that CXCL2 and CXCL3 are crucial in the recruitment, chemotaxis, and proliferation of monocytes and neutrophils during atherosclerosis

progression, mediated by NF- κ B activation, hence facilitating atherosclerosis development [11]. CXCL2 has been documented to expedite the progression of atherosclerosis as a chemokine among inflammatory mediators [126]. CXCL2 is a crucial mediator for neutrophil recruitment and adhesion, which initiates chronic inflammation, the preliminary phase of atherosclerosis. Furthermore, CXCL2 facilitates the firm adhesion of neutrophils, resulting in endothelial dysfunction and plaque development. Literature indicates that neutrophil-released extracellular traps (NETs) can induce the release of interleukin-1 β (IL-1 β) from macrophages, which in turn stimulates T cells to produce the cytokine IL-17, leading to the expression of CXCL1 and CXCL2, thereby enhancing neutrophil recruitment during atherosclerosis and worsening disease progression [127]. Furthermore, a study by Butcher et al. demonstrated that the IL-17 A/IL-17RA pathway exacerbated inflammation in the aortic arch during the atherosclerotic phase by upregulating the expression of aortic CXCL2, hence facilitating the adhesion and migration of neutrophils and monocytes [10]. Figure 4 illustrates the pertinent information.

Obesity

Obesity is characterized by sustained low inflammatory responses, including higher plasma cytokines, increased adipose tissue expression during the acute phase, and activation of pro-inflammatory signaling pathways. Inflammatory chemokines significantly contribute to the promotion of obesity-related adipose tissue

inflammation, with CXCL2 being particularly linked to the progression of obesity. A study demonstrated that CXCL2 expression was markedly increased in mice with obesity induced by a high-fat diet. It was specifically observed that postprandial inflammation was induced by NF- κ B-mediated increases in IL-6 and TNF- α , as evidenced by the overexpression of pro-inflammatory genes CXCL2 in adipocytes [9]. Furthermore, adipose tissue and peripheral blood mononuclear cells (PBMC) in obese persons demonstrate heightened expression of inflammation-associated genes, notably with increased levels of CXCL2 in both adipocytes and PBMC within the obese demographic [128]. Obese mice subjected to a high-fat diet exhibited an elevated risk of wound inflammation [129, 130]. Adipocytes facilitate the secretion of pro-inflammatory cytokines, including IL-6, CXCL2, monocyte chemoattractant protein-1 (MCP-1), and C-reactive protein (CRP). Genetically obese (ob/ob) mice exhibit upregulation of adipocyte differentiation-associated transcription factors, including KLF-5 and peroxisome proliferator-activated CXCL2, in isolated subcutaneous adipose tissue. These data align with the heightened levels of CXCL2 in in vitro-differentiated 3T3-L1 adipocytes [131], indicating a strong association between inflammation in obese adipose tissues and CXCL2. Furthermore, virgin olive oil (VOO) has been shown to downregulate genes in the NF- κ B pathway and specifically diminish the expression of certain inflammatory genes, including CXCL2 [128]. Nonetheless, obesity is associated with the activation of inflammasomes and modified intestinal

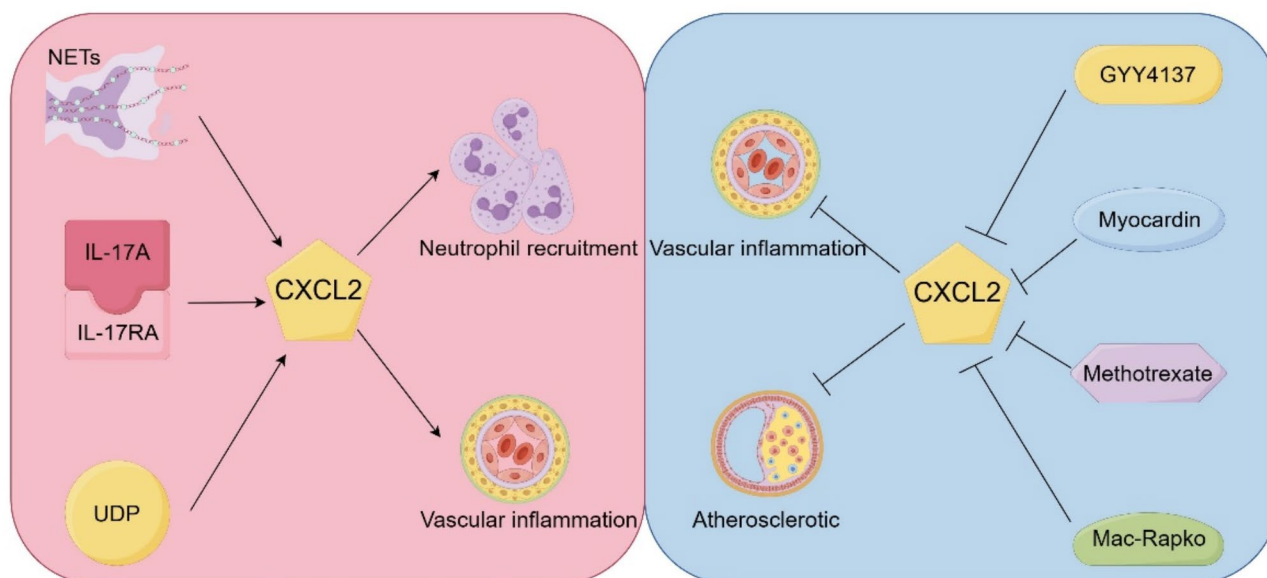


Fig. 4 The function of CXCL2 in the modulation of atherosclerosis. In atherosclerosis, NETs enhance neutrophil recruitment through the up-regulation of CXCL2 expression; the down-regulation of IL-17 A or IL-17RA expression diminishes CXCL2 expression; UDP exacerbates vascular inflammation by inducing CXCL2 expression; GYY4137 and methotrexate decrease CXCL2 expression and mitigate vascular inflammation; myocardial can suppress CXCL2 expression and alleviate vascular endothelial inflammation; Mac-RapKO inhibits CXCL2 expression and impedes the progression of atherosclerosis

Table 2 The key research about the correlation between CXCL2 and atherosclerosis, diabetes, obesity, myocardial infarction, and ischemic stroke

Disease name	Role and mechanism	Reference
Atherosclerosis	UDP binds to P2Y6 and propagates atherosclerosis by inducing the expression of chemokines CXCL2	[132]
Diabetes	Macrophages and b-cells produce the chemokines CXCL2, recruiting CXCR2 expressing neutrophils from the blood to the pancreatic islets. Using CXCR2 antagonist dampens the diabetogenic T-cell response and the later development of autoimmune diabetes	[133]
Obesity	Oral administration of rosiglitazone to wounded obese mice significantly changed subcutaneous adipocyte morphology, reduced wound CXCL2 and Cox-2 expression and improved tissue regeneration	[131]
Myocardial Infarction	Nampt inhibition dampen CXCL2-induced neutrophil recruitment and thereby reduce neutrophilic inflammation- and oxidative stress-mediated tissue damage in early phases of reperfusion after a myocardial infarction	[134]
Ischemic Stroke	Single administration of Evasin-3 during myocardial ischemia significantly reduced infarct size by preventing CXCL2-induced neutrophil recruitment and reactive oxygen species production in myocardial ischemia/reperfusion	[135]

permeability, so the possibility for managing obesity and its comorbidities via CXCL2 requires comprehensive investigation.

CXCL2’s role in inflammation has been documented in numerous studies, with Table 2 enumerating the key research on the association between CXCL2 and atherosclerosis, diabetes, obesity, myocardial infarction, and ischemic stroke.

Challenges and opportunities in targeting CXCL2 therapeutically

While the existing literature provides a comprehensive understanding of CXCL2’s roles in cancer and inflammatory diseases, several critical questions remain unanswered. The dual roles of CXCL2 in tumor progression and suppression, as well as its diverse functions in different inflammatory contexts, highlight the complexity of targeting this chemokine therapeutically. In the following section, we will discuss the challenges and opportunities associated with targeting CXCL2, emphasizing the need for novel strategies and future research directions.

Current therapeutic strategies

The CXCL2/CXCR2 axis has emerged as a promising target for both cancer and inflammatory diseases due to its critical roles in promoting tumor progression and chronic inflammation. Current therapeutic strategies primarily focus on inhibiting CXCR2, as it is a common receptor for multiple ELR+ CXC chemokines, including CXCL2 [21, 22]. Several CXCR2 antagonists have shown potential in preclinical models and early-phase clinical trials, demonstrating reduced tumor growth, metastasis, and immune suppression [79].

Several inhibitors targeting the CXCL2/CXCR2 axis have shown promise in preclinical studies. For example, SB225002, a small-molecule CXCR2 antagonist, has demonstrated significant anti-tumor effects in mouse models of hepatocellular carcinoma by inhibiting neutrophil recruitment and tumor growth [136]. Similarly, AZD5069, another CXCR2 inhibitor, has shown efficacy in reducing neutrophil infiltration and improving outcomes in models of chronic obstructive pulmonary disease (COPD) [137]. These findings highlight the potential of CXCR2 inhibitors as effective therapeutic agents.

Several clinical trials are currently underway to evaluate the efficacy of CXCL2/CXCR2 inhibitors in various diseases. For instance, a Phase I clinical trial of AZD5069 in patients with advanced solid tumors has shown preliminary evidence of safety and tolerability, with some patients experiencing stable disease or partial responses [138]. Another ongoing trial is investigating the combination of SB225002 with standard chemotherapy in patients with metastatic colorectal cancer, aiming to enhance treatment efficacy by targeting the tumor microenvironment [139]. However, the therapeutic landscape for CXCL2 remains underexplored, with limited direct targeting of CXCL2 itself.

Challenges in targeting CXCL2

Compensatory mechanisms

One major challenge in targeting CXCL2 is the potential for compensatory activation of other chemokines that also bind to CXCR2. For instance, inhibiting CXCL2 may lead to increased expression of CXCL1 or CXCL8, which can still activate CXCR2 signaling [4]. This redundancy in the chemokine system complicates the development of effective CXCL2-targeted therapies.

Dual roles in tumor biology

The dual roles of CXCL2 in tumor progression and suppression pose another challenge. While CXCL2 generally promotes tumor growth and immune evasion, it may also contribute to tumor suppression in specific contexts [51]. This complexity requires a nuanced understanding of the tumor microenvironment and the specific roles of CXCL2 in different cancer types and stages.

Heterogeneity in inflammatory diseases

In inflammatory conditions such as atherosclerosis, obesity, and arthritis, CXCL2 drives neutrophil recruitment and exacerbates chronic inflammation [9, 11, 122]. However, the diverse roles of CXCL2 in different inflammatory settings highlight the need for targeted therapies that can selectively modulate CXCL2 signaling without disrupting essential immune functions.

Limited clinical data

Despite preclinical evidence supporting the therapeutic potential of CXCL2/CXCR2 inhibition, clinical trials have been limited, and results have been mixed. Challenges in translating preclinical findings to clinical success highlight the need for better biomarkers and patient stratification strategies to identify those most likely to benefit from CXCL2-targeted therapies [140].

Opportunities for future research

Future research should focus on developing selective inhibitors that can specifically target CXCL2 without affecting other chemokines. This approach may minimize compensatory mechanisms and improve therapeutic efficacy [12]. Then, given the complex roles of CXCL2 in cancer and inflammation, combination therapies targeting CXCL2/CXCR2 alongside other pathways (e.g., immune checkpoint inhibitors or anti-angiogenic agents) may offer synergistic benefits. Preclinical studies have shown promising results in this direction [141]. Identifying biomarkers that predict response to CXCL2-targeted therapies is crucial. These biomarkers could help in patient stratification and personalized treatment strategies, improving the success rate of clinical trials [142]. Exploring CXCL2 in immune modulation may be good research. The dual roles of CXCL2 in tumor biology suggest that it may be possible to harness its tumor-suppressive functions. Future research should explore the mechanisms underlying CXCL2-mediated tumor suppression and identify ways to enhance these effects therapeutically [51]. In inflammatory conditions, targeting CXCL2 may offer a novel approach to modulating neutrophil recruitment and reducing chronic inflammation. Future studies should focus on understanding the specific roles of CXCL2 in different inflammatory diseases and developing targeted therapies to mitigate its pro-inflammatory effects [9, 11].

Novel hypotheses

We hypothesize that CXCL2 may act as a context-dependent tumor suppressor in certain genetic backgrounds or microenvironments. Future studies should investigate the specific conditions under which CXCL2 exerts tumor-suppressive effects and identify potential therapeutic strategies to exploit this duality [51]. Another hypothesis

is that CXCL2 may play a critical role in immune-evasion mechanisms in certain tumors. Targeting CXCL2 in combination with immunotherapies may enhance immune surveillance and improve patient outcomes [141]. Given the role of CXCL2 in obesity-related inflammation, we propose that targeting CXCL2 may offer therapeutic benefits in metabolic diseases. Future research should explore the potential of CXCL2 inhibitors in modulating metabolic inflammation and improving insulin sensitivity [9].

In summary, the CXCL2/CXCR2 axis represents a promising therapeutic target with potential applications in cancer and inflammatory diseases. Ongoing clinical trials and preclinical studies continue to explore the full potential of this pathway, paving the way for novel and effective treatment strategies.

Discussion

CXCL2, a pivotal chemokine within the tumor microenvironment, is produced by both tumor parenchymal and mesenchymal cells. It plays a crucial role in modulating the interactions between these cells, thereby influencing tumor progression. CXCL2 activates key intracellular signaling pathways, including ERK/MAPK, PI3K/AKT, and JAK2/STAT3, which collectively drive cell survival, motility, and metastasis. Given its multifaceted role in tumor biology, the CXCL2/CXCR2 signaling axis is emerging as a promising therapeutic target for both cancer and inflammatory diseases.

In the context of cancer pathogenesis, inflammation is increasingly recognized as a driving force that significantly impacts tumor development and disease progression [143]. Local immune responses and systemic inflammatory processes can profoundly influence the clinical presentation and prognosis of cancer patients. In this regard, CXCL2-mediated inflammatory signaling is particularly noteworthy. By orchestrating the recruitment of immune cells and promoting an immunosuppressive microenvironment, CXCL2 contributes to tumor growth and malignant transformation [122, 144]. This highlights the potential of CXCL2 as a therapeutic target for disrupting the tumor-promoting inflammatory milieu.

Current therapeutic strategies targeting the CXCL2/CXCR2 pathway predominantly focus on inhibiting CXCR2, rather than directly suppressing CXCL2 synthesis or secretion. This approach is informed by the compensatory activation of alternative chemokine ligands within CXCR2 signaling, which suggests that targeting the receptor may offer broader therapeutic benefits. However, despite growing interest in the CXCL family of chemokines, research specifically targeting CXCL2 remains limited. This gap in knowledge underscores the need for further investigation into the precise role of CXCL2 in tumorigenesis and its underlying molecular

mechanisms. While it is established that CXCL2 levels are elevated in various cancers, including breast, colon, and stomach cancers, and correlate with poor prognosis, the detailed mechanisms through which CXCL2 exerts its effects remain unclear. Additionally, the biological origin of CXCL2, its functions within the tumor microenvironment, and its interactions with immune cells require further elucidation. Understanding the upstream regulatory mechanisms, particularly the transcription factors that control CXCL2 expression, will be crucial for developing targeted therapies.

Beyond cancer, CXCL2 is a multifunctional chemokine that plays a significant role in the body's inflammatory response. Its involvement in various inflammatory diseases highlights its potential as a therapeutic target in these contexts as well. Future research should focus on unraveling the diverse mechanisms of CXCL2 action and developing intervention strategies that target CXCL2 or its associated signaling pathways. This will not only enhance therapeutic outcomes but also improve the quality of life for patients suffering from inflammatory disorders. Moreover, considering the connections between CXCL2 and other signaling pathways will be essential for formulating comprehensive therapeutic strategies.

In summary, the CXCL2/CXCR2 pathway holds significant promise for targeted cancer treatments and the management of inflammatory diseases. By disrupting the CXCL2-mediated inflammatory and tumorigenic processes, we may be able to halt early tumor growth, mitigate chronic inflammation, and ultimately improve patient outcomes. Further exploration of the CXCL2 signaling axis will undoubtedly contribute to both the theoretical understanding and clinical application of these diseases.

Author contributions

YHL: Writing - original draft, Writing - review & editing. CZC: Writing - original draft. MMH: Writing - original draft. CFT: Writing - original draft. FYS: Writing - original draft. SJF: Writing - original draft. MMX: Writing - original draft. ZYZ: Writing - original draft. HYZ: Writing - original draft. WS: Conceptualization, Visualization, Writing - review & editing. JTZ: Supervision, Visualization, Writing - original draft, Writing - review & editing. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics and Consent to participate

Not applicable.

Informed consent

Not applicable.

Competing interests

The authors declare no competing interests.

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