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The role of CXCR2 in acute inflammatory responses and its antagonists as anti-inflammatory therapeutics

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Abstract

Purpose of review—CXCR2 is key stimulant of immune cell migration and recruitment, especially of neutrophils. Alleviating excessive neutrophil accumulation and infiltration could prevent prolonged tissue damage in inflammatory disorders. This review focuses on recent advances in our understanding of the role of CXCR2 in regulating neutrophil migration and the use of CXCR2 antagonists for therapeutic benefit in inflammatory disorders.

Recent findings—Recent studies have provided new insights into how CXCR2 signaling regulates hematopoietic cell mobilization and function in both health and disease. We also summarize several CXCR2 regulatory mechanisms during infection and inflammation such as via Wip1, T-bet, P-selectin glycoprotein ligand-1, granulocyte-colony-stimulating factor, and microbiome. Moreover, we provide an update of studies investigating CXCR2 blockade in the laboratory and in clinical trials.

Summary—Neutrophil homeostasis, migration, and recruitment must be precisely regulated. The CXCR2 signaling pathway is a potential target for modifying neutrophil dynamics in inflammatory disorders. We discuss the recent clinical use of CXCR2 antagonists for controlling inflammation.

Keywords

CXCR2; CXCR2 antagonist; infection; inflammation; neutrophils

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Conflicts of interest

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INTRODUCTION

Chemokines are a large family of signaling proteins that mediate cellular migration, especially of immune cells. CXCR2 is mainly expressed on neutrophils, monocytes, natural killer cells, mast cells, and endothelial cells, and is the receptor for CXC chemokine ligands, especially CXCL8 [1]. CXCR2 mediates a G-protein-coupled receptor (GPCR) signaling cascade, with its activation starting with dissociation of the receptor from the G-protein, followed by release of the Gβ subunit from the Gα subunit [2]. It has been shown that CXCR2 is phosphorylated by GPCR kinases after activation, which triggers dynamin-mediated and clathrin-mediated receptor internalization mediated by β-arrestin1/2 and AP-2 [3]. Activated CXCR2 induces calcium release, activation of the Ras/MAPK, and PI3K signaling cascades, and it is involved in many immune responses including directed neutrophil migration [4]. Recently, Del Prete *et al.* [5■■] reported that CXCR2-mediated neutrophil recruitment to sites of inflammation can be regulated by CCRL2, a seven-transmembrane domain receptor that shares structural and functional similarities with atypical chemokine receptors. CCRL2/CXCR2 heterodimerization regulates membrane CXCR2 expression and function, providing a novel mechanism for its regulation. For example, CXCR2-mediated signaling was impaired in CCRL2-deficient neutrophils.

Neutrophils express over 30 receptor types including pattern recognition receptors, cytokine receptors, adhesion receptors, and GPCRs [6]. They play a central role in innate immunity via sensing various stimuli through these receptors, acting as the first line of host defense against infection. Neutrophils migrate to sites of infection to then control bacterial burden. A recent study suggests that neutrophil recruitment during inflammation proceeds in two phases: an early phase, mediated by short-lived signals, followed by an amplification phase to prolong neutrophil recruitment and activation, which is mediated by signaling cascades through leukotriene-B4 and CXCL8-family chemokines [7,8]. Excess neutrophil infiltration can enhance the inflammatory response and prolong tissue damage [9-11]. Balancing pathogen control and inflammation-related tissue injury is largely dependent upon neutrophil homeostasis as well as the degree of neutrophil activation in the presence of various stimuli. Regulating neutrophil CXCR2 and its ligand expression are potential therapeutic targets for controlling neutrophil recruitment and function in inflammatory disorders.

THE EFFECT OF CXCR2 SIGNALING ON HEMATOPOIETIC CELL MOBILIZATION AND RECRUITMENT

CXCR2 is known to be involved in neutrophil recruitment from peripheral blood to inflamed tissue. Chou *et al.* illustrated the amplification stage of neutrophil recruitment in an inflammatory arthritis modal and showed that cytokines such as IL-1β and chemokines such as CXCL12 released by activated neutrophils activate synovial cells. These activated synovial tissues then produced ligands for CXCR1 and CXCR2 to further promote sequential neutrophil activation [12]. CXCR2 is also responsible for neutrophil migration to tumors in mouse cancer models. Significantly, CXCR2 expression was significantly lower in tumor-associated neutrophils than those in the bone marrow and peripheral blood [13], with endogenous IFN-β inhibiting CXCR2-induced neutrophil recruitment by reducing CXCR2

ligand expression and chemokine gradients. Bian *et al.* recently reported myeloid-derived suppressor cells (MDSCs) with high CXCR2 expression that promoted tumor progression. These G-MDSCs were functionally different to mature neutrophils and accumulated in tumors to immunosuppress T cells [14■].

The role of CXCR2 in neutrophil migration from bone marrow to peripheral blood has also been well explored. ELR^+ chemokines such as CXCL8 stimulated neutrophil mobilization in a CXCR1-dependent and CXCR2-dependent manner [15]. In addition, neutrophils lacking CXCR2 have impaired emigratory capacity [16]. Eash *et al.* [17] showed that CXCR2 signaling antagonized CXCR4 to regulate neutrophil release from the bone marrow. More recently, granulocyte-colony-stimulating factor (G-CSF) and CXCR2 have been shown to interact during inflammation. G-CSF is a well known neutrophil-mobilizing cytokine [18], and its mobilization function is believed to be mediated by CXCR2 ligands [19], as G-CSF failed to mobilize neutrophils in CXCR2-deficient mice. In an arthritis modal, anti-G-CSF receptor blockade not only significantly reduced cell adhesion in joints, but also reduced CXCR2-expressing circulating neutrophils [20■]. On the other hand, the activation of CRCR2 can also be modulated by G-CSF. Compared with G-CSF, CXCR2-induced neutrophil mobilization much more quickly [21,22], indicating a distinct mobilization mechanism. Bajrami *et al.* [23■■] revealed that *Escherichia coli*-induced G-CSF increases during the early stages of inflammation inhibited rapid CXCR2-mediated neutrophil mobilization. G-CSF was elevated after CXCR2 ligands macrophage inflammatory protein 2 and keratinocyte chemoattractant were expressed, and this elevation inhibited CXCR2-mediated neutrophil chemotaxis. Further, only CXCR2-induced neutrophil mobilization from the bone marrow was suppressed by G-CSF and not other chemoattractants such as leukotriene-B4, C5a, or fMLP. The regulatory function of G-CSF on CXCR2 signaling indicated that exaggerated neutrophil mobilization may be achieved by targeting G-CSF-elicited pathways.

CXCR2 signaling has also been implicated in the mobilization of hematopoietic stem/progenitor cells (HSPCs). Clinically, HSPCs are usually mobilized from the bone marrow to peripheral blood using a G-CSF regimen. The effect of CXCR2 on HSPC mobilization was first reported about 10 years ago [22]. More recently, Hoggatt *et al.* [24■■] reported an alternative HSPC mobilization regimen, a combination of GROb and AMD3100 (a CXCR2 agonist and a CXCR4 antagonist, respectively), which increased HSPC mobilization by elevating matrix metalloproteinase 9. Importantly, the new regimen displayed better engraftment and greater donor chimerism compared with the G-CSF regimen.

THE ROLE OF CXCR2 IN INFECTION AND INFLAMMATION

As noted above, neutrophils can migrate and recruit to inflamed sites under the control of CXCR2 during infection to exert their antimicrobial function. CXCR2 expression on neutrophils is downregulated during sepsis. Significantly, disruption of phospholipase D2 significantly upregulated CXCR2 expression in septic mice, increasing bactericidal activity, decreasing vital organ damage, and improving survival during experimental sepsis [25]. In another study, Shen *et al.* [26■] demonstrated that inhibition of wild-type p53-induced phosphatase 1 attenuated CXCR2 internalization and improved sepsis outcomes in mice. In

addition, a negative relationship between neutrophil CXCR2 and Wip expression has also been observed in septic patients. Although CXCR2 signaling is clearly required for host defense responses, in a modal of *Staphylococcus aureus*-induced septic arthritis, delayed CXCR1/2 blockade effectively controlled the articular inflammatory damage without compromising antibacterial responses [27■].

Inflammation, including neutrophil adhesion to lesional vascular endothelial cells, contributes to deep vein thrombosis. Yago *et al.*[28■■] demonstrated that synergy between P-selectin glycoprotein ligand-1 and CXCR2 on rolling neutrophils increased neutrophil adhesion and procoagulant neutrophil extracellular trap (NET) release, increasing thrombus frequency and size. Gollomp *et al.*[29■] investigated the molecular mechanism of NETs during thrombosis development in a heparin-induced thrombocytopenia model. They showed that neutrophils migrated via a CXCR2-dependent mechanism to accumulate in thrombi, and CXCR2 antagonist therapy reduced neutrophil counts in thrombi with clinical significance.

The role of CXCR2 signaling in other inflammatory diseases has also been investigated in recent years. CXCR2 has been considered as a potential pharmacological target in controlling inflammatory damage in the pathogenesis of chronic obstructive pulmonary disease (COPD) [30,31], asthma [32], arthritis [20■], and hepatitis [33,34]. Hoegl *et al.* [35■] reported that reduced CXCR2 chemokines were related to attenuated endotoxin-induced lung injury in *Tbet*$^{-/-}$ mice. There are also intriguing associations between the microbiome and susceptibility to amebiasis infection, with dysbiosis increasing the susceptibility and severity of amebiasis infection, with fewer infiltrating cecal neutrophils and diminished CXCR2 expression [36■■]. These results suggest that the interaction between neutrophils and the microbiome may be a promising target in colitis treatment and emphasize the role of CXCR2 in regulating intestinal neutrophil recruitment.

CXCR2 BLOCKADE IN ACUTE INFLAMMATION

Several attempts have been made to regulate neutrophil migration and recruitment to control inflammatory diseases. The role of CXCR2 in regulating neutrophil recruitment is now better established, especially through the use of CXCR2 knockout strategies [37]. Hence, blocking CXCR2 signaling, including with CXCR2 antagonists, chemokine analogs, and CXCR2 receptor antibodies, has been applied to inflammatory diseases [37]. Several different CXCR2 antagonist structures exist: diarylurea and its analogs, compounds in which urea is replaced with squaramide, pyrimidine-based compounds, and bicyclic pyrimidine compounds. Of these, the diarylurea compounds were the first to be described. These different structures provide varying improvements in oral bioavailability, receptor selectivity, and tolerance [38].

Some popular CXCR2 antagonists are listed in Table 1, and those in clinical trials are summarized in Table 2. The types of CXCR2 blockers are wide with similarly diverse indications, including COPD, bronchiectasis, asthma, nephropathy, pancreatitis, and cancer. Taking respiratory inflammation as an example, AZD5069 has been reported to reduce airway neutrophilia [39■,40]. However, safety remains of concern, with clinical results

showing that even though neutrophil immunoprotection was not compromised during CXCR2 inhibition [39■], this neutrophil-targeted therapy still increased infection susceptibility.

CONCLUSION

It is now well established that CXCR2 is a crucial regulator of hematopoietic cell homeostasis, migration, and recruitment, and is implicated in a variety of inflammatory diseases and cancer. Therefore, CXCR2 and its related signaling pathways could be promising pharmacological targets in these diseases. Efforts still need to be made to fully understand the pathophysiological role of CXCR2 signaling in health and disease and to define optimal regimens with improved compounds with ideal pharmacokinetics, treatment timing, and clinical responses.

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KEY POINTS

- CXCR2 is a crucial regulator of hematopoietic cell homeostasis, migration, and recruitment, and is implicated in a variety of inflammatory diseases and cancer.
- CXCR2 expression and activation are tightly regulated during infection and inflammation.
- CXCR2 and the related signaling pathways could be promising pharmacological targets in various infections and inflammatory diseases.
- Efforts still need to be made to fully understand the pathophysiological role of CXCR2 signaling in health and disease and to define optimal regimens with improved compounds with ideal pharmacokinetics, treatment timing, and clinical responses.

Table 1.

Commonly used CXCR2 chemical antagonists

Name	Structure	Model	Therapeutic use or clinical trial	Reference
Danirixin	1-[4-chloro-2-hydroxy-3-[(3S)-piperidin-3-yl] sulfonylphenyl]-3-(3-fluoro-2-methylphenyl)urea	Rat	Phase II for COPD	[41-43]
SCH527123 (MK-7123)	2-hydroxy-N,N-dimethyl-3-[[2-[[(1R)-1-(5-methylfuran-2-yl)propyl]amino]-3,4-dioxocyclobuten-1-yl]amino]benzamide	Mouse, rat	Phase II for COPD, asthma, traumatic brain injury, breast cancer, pancreatic cancer, acute-on-chronic liver failure	[44-46]
Reparixin	(2R)-2-[4-(2-methylpropyl)phenyl]-*N*-methylsulfonylpropanamide	Rat, mouse, and pig	Phase II for kidney and lung transplantation, metastatic breast cancer; Phase III for pancreatic islet transplantation in type 1 diabetes	[47-51]
AZD5069	*N*-(2-((2,3-difluorobenzyl)thio)-6-(((2R,3S)-3,4-dihydroxybutan-2-yl)oxy)pyrimidin-4-yl)azetidine-1-sulfonamide	Monkey	Phases Ib and II for head and neck cancer, metastatic castration-resistant prostate cancer; Phase II for asthma, COPD, bronchiectasis, coronary artery disease	[39■,52-55]
AZD8309	(R)-5-[[(2,3-difluorophenyl)methyl]thio]-7-[(2-hydroxy-1-methylethyl)amino]-thiazolo[4,5-d]pyrimidin-2(3H)-one	Mouse	Phase I for rheumatoid arthritis, COPD, pancreatitis	[56,57]
G31P	6-Chloronicotinamide N-oxide 4a	Mouse, rat, and guinea pig	Aspiration pneumonia; ischemia and reperfusion injury; lung cancer; mastitis lesions; diabetic nephropathy; UAN kidneys; hepatocellular carcinoma; prostate cancer; ulcerative colitis	[58-61]
Ladarixin	(1,1-dioxo-1λ6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone	Mouse	Type 1 diabetes	[62]

COPD, chronic obstructive pulmonary disease; UAN, uric acid nephropathy.

Table 2.

Summary of CXCR2 blockade strategies being used in registered clinical trials

CXCR2 blockade	Clinical trial	Identifier
AZD5069	Phases Ib and II for head and neck cancer	
	Phases Ib and II for metastatic castration-resistant prostate cancer	
	Phases Ib and II for metastatic pancreatic Ductal adenocarcinoma	
	Phase II for asthma	
	Phase II for COPD	
	Phase II for bronchiectasis	
Danirixin	Phase II for COPD	
SCH527123 (MK-7123)	For solid tumors (nonsmall-cell lung cancer, castration-resistant prostate cancer, and microsatellite stable colorectal cancer)	
AZD8309	The effect on cells and inflammatory biomarkers after nasal challenge with LPS	
Reparixin	Phase I for metastatic breast cancer	
	Phase II/III for pancreatic islet transplantation in type 1 diabetes mellitus	
	Phase II for ischemia-reperfusion injury in liver transplantation	
	Phase II for breast cancer	
	Phase II for pancreatectomy for chronic pancreatitis	
	Phase II for ischemia-reperfusion injury kidney diseases	
	Phase II for ischemia-reperfusion injury lung transplantation	
Ladarixin	Phase II for new-onset type 1 diabetes	

COPD, chronic obstructive pulmonary disease; LPS, lipopolysaccharide.