Minireview

Blockade of CXCR2 signalling: A potential therapeutic target for preventing neutrophil-mediated inflammatory diseases

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Abstract

Polymorphonuclear neutrophils (PMN) play a key role in host innate immune responses by migrating to the sites of inflammation. Furthermore, PMN recruitment also plays a significant role in the pathophysiology of a plethora of inflammatory disorders such as chronic obstructive pulmonary disease (COPD), gram negative sepsis, inflammatory bowel disease (IBD), lung injury, and arthritis. Of note, chemokine-dependent signalling is implicated in the amplification of immune responses by virtue of its role in PMN chemotaxis in most of the inflammatory diseases. It has been clinically established that impediment of PMN recruitment ameliorates disease severity and provides relief in majority of other immune-associated disorders. This review focuses on different novel approaches clinically proven to be effective in blocking chemokine signalling associated with PMN recruitment that includes CXCR2 antagonists, chemokine analogs, anti-CXCR2 monoclonal antibodies, and CXCR2 knock-out models. It also highlights the significance of the utility of nanoparticles in drugs used for blocking migration of PMN to the sites of inflammation.

Keywords: Chemokine analogs, CXCR2 antagonists, integrins, neutrophil infiltration, PMN, selectins, transmigration

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Introduction

Polymorphonuclear neutrophils (PMN) represent the most abundant subset of leukocytes that play a pivotal role in innate immune responses,[1,2] and are amongst the first cells to arrive at the site of inflammation via chemotaxis following sensing of danger-associated molecular patterns (DAMPs) released by injured or infected cells. PMN migration across the blood vessels to the site of injury is a sequential, multistep process driven by a myriad of endothelial and leukocyte-expressed adhesion molecules, for instance, selectins, integrins, chemokines, platelet/endothelial-cell adhesion molecule-1 (PECAM-1), intercellular adhesion molecule-1 (ICAM-1), junctional adhesion molecule (JAM), and DAMP/pathogen-associated molecular patterns (PAMPs), which represent the hallmark of acute inflammation.[1,2] Better understanding of the chemokine receptors and their interaction with cognate ligands could shed more light on the prevention and treatment of inflammatory disorders.

Chemokine signalling reportedly regulates PMN trafficking by aiding in the activation, adhesion, crawling and egress of PMNs across the endothelial barrier.[3] Notably, CXCL8 is one major chemokine that binds to CXCR1 and CXCR2 receptors, and drives the onset of tumor,[4] rheumatoid arthritis (RA)[5,6] and inflammatory bowel disease (IBD).[7–9] Therefore, inflammatory responses could essentially be ameliorated by attenuating PMN recruitment via blockade of chemokine signalling.[7,10,11] CXCR1 represents a class A rhodopsin-like G-protein coupled receptor (GPCR) responsible for cellular signal transduction. The gene that encodes CXCR1 protein is present on 2q35 chromosome that is comprised of two exons set apart by an intron.[12,13] The molecular structure of CXCR1 is comprised of seven transmembrane helices (TM1–TM7) connected by three intracellular and three extracellular hydrophilic loops. CXCR2

represents another structurally and functionally similar GPCR molecule that triggers chemokine signalling via a tyrosine sulfation motif. The cDNA of CXCR2 was first cloned from HL-60 cells by Murphy and Tiffany.[14] The gene that encodes CXCR2 is also present on the 2q35 chromosome, and encodes a protein that contains 360 amino acids. CXCR2 gene consists of 3 exons interspersed by introns having a molecular weight of 3 and 5.4 kb.[15] Human CXCR1 and CXCR2 are mostly homogenous (77% amino acid identity) except at three distinct regions, the C-terminus, N-terminus, and the transmembrane domains.[16,17] Ligands interacting with CXCR1 include CXCL1, CXCL6, and CXCL8, which could also bind to CXCR2. Further, CXCL2, CXCL3, CXCL4, CXCL5, and CXCL7 also bind to CXCR2. *N*-acetyl proline-glycine-proline (PGP), an extracellular membrane (ECM) breakdown product reportedly binds to both CXCR1 and CXCR2 on human PMNs.[18]

CXCR1 is expressed in the adrenal gland, thyroid gland, prostate gland, lungs, liver, PMNs, mast cells, and fibroblasts.[10,19–22] CXCR2 is expressed in the brain, craniofacial tissues, lungs, spinal cord, liver, kidney, PMNs, lymphocytes, endothelial cells, and bronchoepithelial cells.[10,23–32] CXCR2 expression is pivotal in certain pathological conditions, and therefore characterizing its role in disease pathogenesis could assist in designing newer anti-inflammatory therapeutic strategies. CXCR1 and CXCR2 signalling plays a pivotal role in the antimicrobial functions of PMNs, especially chemotaxis, degranulation, phagocytosis, and oxidative burst. Signalling via these receptors occurs via GTP proteins, which further leads to downstream events viz., PLC activation, calcium mobilization, activation of PKB (Akt), MAPK, and ERK 1/2 pathways[10] (Figure 1).

CXCR2 functional homologue is present on chromosome 1C3 in rats and mice (in contrast to absence of CXCR1) making it easier to work with disease models of disorders that target CXCR2 in gene knock-out investigations to better correlate with disease pathogenesis.[10] Multiple ligands bind CXCR2 exclusively, but none bind CXCR1 exclusively suggesting that CXCR2 alone, but not CXCR1 could be involved in the activation of PMNs. This indicates that blockade of CXCR2 may have clear consequences in ameliorating certain inflammatory manifestations, opening up novel frontiers in the development of immunotherapeutics.

Investigations employing CXCR2 knock-out strategies have clearly established the role of CXCR2 in PMN-associated inflammation and other disease states. Some of the studies that describe the use of animal models in disease pathogenesis are outlined in Table 1. CXCR2 knock-out models are used to characterize the importance of PMNs in colitis and sepsis. CXCR2-knock-out mice showed reduced PMN migration into the lungs resulting in decreased lipopolysaccharide (LPS)-induced inflammation of the lungs.[33] Inhibition of chemokine ligands in several other disorders like keratitis, lung injury, airway inflammation and septic injury resulted in decreased or complete inhibition of PMN recruitment leading to marked alleviation of disease symptoms.[10]

Diverse approaches in blockade of chemokine signalling

CXCR2 has broader constitutive functions in the pathophysiology of disease manifestations.[34] CXCR2 and its cognate ligands are implicated in a variety of inflammatory disorders making it an interesting entity for potential therapeutic approaches. CXCR2 blockade leads to translocation and inhibition of PMN migration to the sites of inflammation. Distinct strategies like CXCR2 antagonists, chemokine analogs, and antibodies to CXCR2 receptor have been experimentally tested in small animals for blocking CXCR2, and could be used as therapeutic options against inflammatory diseases (Tables 1–4). The approaches used in the blockade of CXCR2 in different cell and animal models have been briefly elucidated by different commercial agencies like Dompé pharmaceuticals, GlaxoSmithKline (SmithKline-Beecham), and AstraZeneca PLC. The interaction of different chemical/antibody blockers with CXCR1 and CXCR2 molecules followed by downstream signals leading to appropriate therapeutic effects are shown in Figure 1.

CXCR2 antagonism

Selective antagonism of the interaction between CXCR2 and its various cognate ligands serves as a potential strategy for altering PMN recruitment to various tissues, which results in the abatement of progression to a coterie of inflammatory manifestations.[35] Recognition of the efficacy of smaller molecular antagonists in the treatment of inflammatory diseases has led to extensive research culminating in the discovery of a myriad of CXCR2 antagonists. A list of CXCR2 antagonists discovered following extensive research over the years has been summarized in Table 2.

The first ever discovered CXCR2 antagonist, identified using a high throughput screening (HTS) program was SKF-83589 by GlaxoSmithKline that belongs to the class of diaryl urea. It is a moderately potent inhibitor that displaces CXCL8 binding to CXCR2. SKF-83589 has shown marked *in vitro* efficacy in human and rabbit PMN functional assays.[36] By using combinatorial techniques, SKF-83589 has been chemically optimized by randomly placing substituents on both the aromatic rings resulting in the discovery of a more potent compound, SB225002.[37] SB225002 reportedly inhibits interleukin-8 (IL-8) binding to CXCR2 and was selective by ~150-fold against CXCR1 and other GPCRs.[38] In addition, SB225002 also appears to inhibit human and rabbit PMN chemotaxis induced by both CXCL8 and CXCL1 but lacked oral activity in animal models, in addition to having poor pharmacokinetic properties.

SAR evaluation of the compound involving bioisostere replacement by substituting hydroxyl group with triazole ring has led to the identification of SB265610, which appears to be more potent than SB225002.[36] SB265610 has more oral bioavailability and better *in vivo* functions as evident from animal experimentations. Interestingly, it is found to be also effective in ameliorating atherosclerotic lesions and LPS-induced neutrophilia.[39] Other lead compounds in the urea

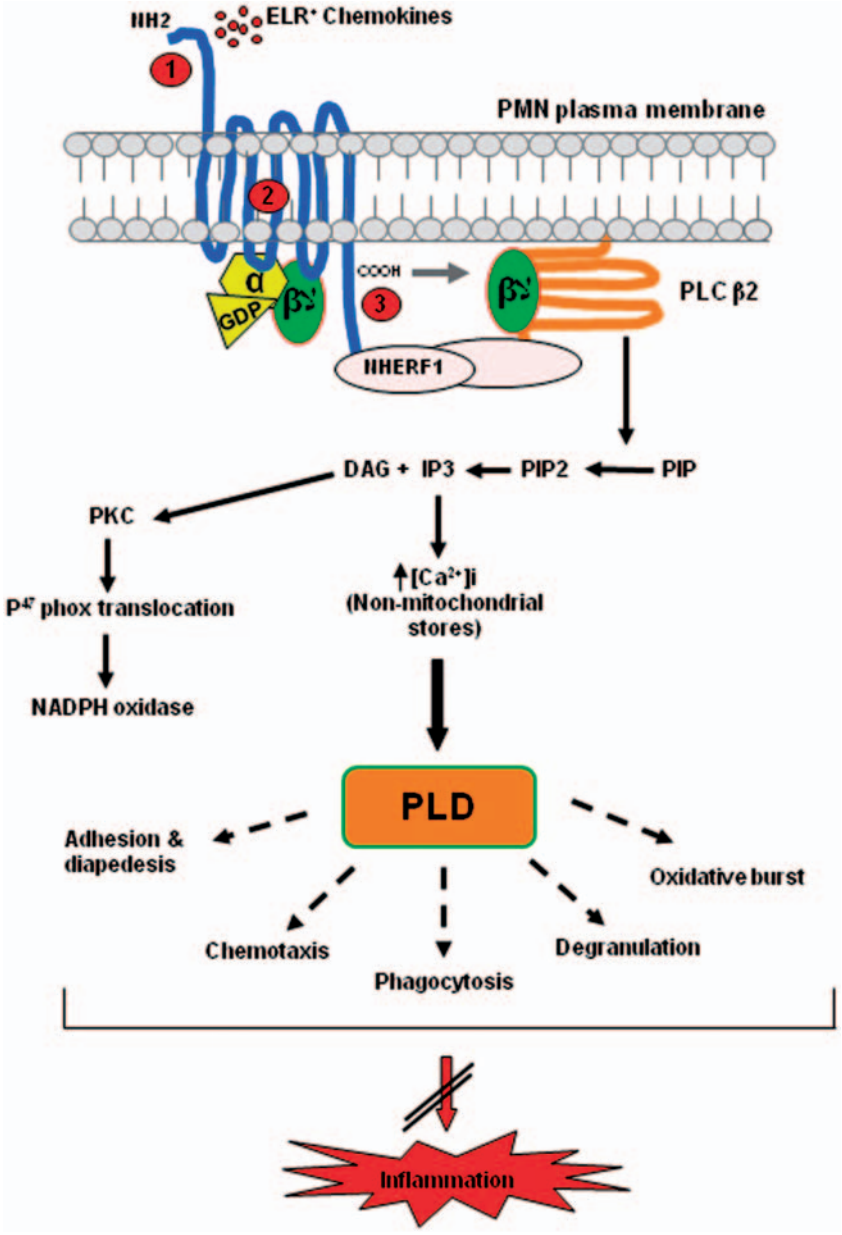

Figure 1 Role of CXCR1/2 antagonists in the prevention of inflammatory disorders. CXCR1/2 on PMNs are activated via binding of ELR+ ligands. Excessive recruitment of PMNs cause inflammation and tissue injury. CXCR1/2 antagonists block and inhibit PMN recruitment and release toxic substances that prevent inflammation and associated tissue injuries. N-terminal antagonists are targeted towards (1) Ligand-binding sites of their cognate receptors, for instance, chemical inhibitors SB225002 [94] or neutralizing antibodies [7]; (2) Binding to the allosteric site located on the transmembranes of the CXCR1/2 and non-competitively inhibiting ligand binding Eg. Repertaxin [95] and DF2162 [96]; (3) Curtailing the functions of C-terminal tail of the receptor by blocking or disrupting the C-terminal trimeric macromolecular complex (CXCR2-NHERF1-PLC-b2) via delivering C-terminal peptide [97] or using allosteric inhibitors. Eg. SB265610 and sch527123 [98] PLD, phospholipase C; PLC, phospholipase C; IP3, inositol 1, 4, 5-trisphosphate; DAG, diacylglycerol; PIP2, phosphatidylinositol 4,5-bisphosphate; [Ca2+]i, intracellular calcium concentration; NADPH oxidase, Nicotinamide adenine dinucleotide phosphate oxidase; NHERF1, Na(+)/H(+) exchange regulatory cofactor 1; PKC, protein kinase C. (A color version of this figure is available in the online journal.)

series are SB332235 and its analog SB656933, which have shown greater abilities in inhibiting CXCL8-binding to CXCR2 with relatively better pharmacokinetic profiles. SB332235 has also been reported to significantly reduce PMN migration into the synovial compartment of acute arthritis rat models.[40] SB656933 and Sch527123 have recently been reported to inhibit PMN infiltration in chronic obstructive pulmonary disease (COPD).[41]

In recent years, several drugs of different classes like thioureas, guanidines, and sulfonamides have been claimed to inhibit PMN extravasation by blocking CXCL8 binding to CXCR2, but are undergoing clinical trials, and therefore, the mechanisms are yet to be declared.[42] Increasing interest in CXCR2 antagonists has promoted AstraZeneca to launch a campaign for discovering better novel CXCR2 antagonists. AstraZeneca has discovered fused pyrimidine-based

Table 1 Summary of animal models of inflammatory disease showing the significance of blockade of CXCR2 using knock-out strategies or antibodies specifically targeting CXCR2 receptor

Approach	Disease	Model	Therapeutic effect	Ref.
CXCR2 antibodies	TNBS-induced colitis	Rats	Decreases PMN infiltration into colon of colitis rats after 8hrs	65
	BOS	Mice	Inhibits early PMN infiltration and vascular remodeling to attenuate BOS	66
	dsRNA-induced lung injury		Attenuates PMN sequestration and lung injury	56
CXCR2 knock-out and antibodies	DSS-induced acute colitis	Mice	Reduces PMN infiltration into mucosa resulting in resolution of ulcers	7
CXCR2 knock-out	DSS-induced chronic colitis	Mice	Inhibits PMN infiltration resulting in reduced mucosal damage	67
	Septic injury		Delays PMN recruitment protecting against sepsis	68
	Ozone-induced airway inflammation		Decreases PMN migration in BALF in airway spaces	38
	Helminth-mediated keratitis		Decreases PMN migration to central cornea alleviating corneal inflammation	69

BALF, bronchoalveolar lavage fluid; BOS, bronchiolitis obliterans syndrome; DSS, dextran sodium sulphate.

CXCR2 antagonists like AZ8309 against RA and COPD.[41] AZ8309 has been shown to inhibit neutrophilic infiltration of the lungs and elastase activities of PMNs in the sputum.[44] Subsequently, AstraZeneca has also developed a bicyclic CXCR2/CCR2 antagonist AZ10397767, a thiazolopyrimidine compound that has shown relatively better oral bioavailability but relatively shorter clearance in rats.

Certain other classes of CXCR2 antagonists like nicotinamide-*n*-oxides and 4-fluoro nicotinanilides are currently being developed by Celltech Group PLC.[36] These compounds selectively inhibit growth-regulated oncogene alpha (GRO-α)-driven human PMN chemotaxis for potential use against acute inflammatory, autoimmune, and allergic disorders resulting from PMN chemotaxis.[45,46] A new class of CXCR2 antagonists has been developed recently. These CXCR1/CXCR2 allosteric inhibitors act by curtailing PMN activation rather than by inhibiting the binding of ligands to CXCR2 receptor. *Dompé* Pharma (Italy) has launched a program primarily to identify potent allosteric inhibitors for the treatment of reperfusion/post-ischemia. It was aimed at investigating a class of 2-arylphenyl propionic acids, and has resulted in the discovery of reparixin (repertaxin), a ketoprofen derivative, which inhibits CXCL8-induced PMN activation.[81] Reparixin is used intravenously as its pharmacokinetics does not allow oral delivery,[43] and is currently being used in clinical trials assessing its efficacy in the prevention of graft functions following kidney or lung transplantation. Reparixin acts by modulating PMN recruitment and eventual onset of tissue damage in experimental models of ischemia/reperfusion injury.[47]

Dompé has developed structurally similar compounds like DF2162 possessing equivalent activity with both CXCR1 and CXCR2. DF2162 has an extended in vivo half-life with excellent oral bioavailability as measured in rodents, and inhibits both CXCL1- and CXCL8-mediated PMN chemotaxis.[6,48] Besides, it has also shown remarkable efficacy in a variety of pulmonary inflammatory manifestations. DF2156-A is another noncompetitive inhibitor, which reportedly blocks CXCR1/CXCR2 signal transduction leading to chemotaxis.[49] Apart from alleviating CXCR1/CXCR2-mediated acute and chronic inflammation, DF2156-A also improves neurological functions in rat models. More recently, a potent CXCR1/2 inhibitor SCH527123 has been introduced by Schering–Plough, which acts by inhibiting the activation and trafficking of PMN in animal models, especially against inflammatory disorders involving the lung.[50]

GlaxoSmithKline has advanced its stride into discovering a plethora of CXCR2 antagonists and using them in clinical trials. SB468477 is a cyanoguanidine compound that inhibits chemokine binding to both CXCR1 and CXCR2. GSK1325756 developed against COPD, is another CXCR2 antagonist that has been tested in phase I clinical trial in healthy adult volunteers (www.clinicaltrials.gov, number NCT01267006). The study involved administering the individuals either with a placebo or GSK1325756 and investigating the various blood parameters. Apart from these antagonists, a myriad of other potent antagonists have been discovered, namely imidazolyl pyrimidine derivatives,[51] diaryl isoxazoles,[52] and ketoprofen isomers,[53] but remains to be tested in trials for determining clinical efficacy.

Chemokine analogs

Chemokine analogs are molecules that does not transduce signals, but are mutated to bind to CXCR2 leading to inhibition of PMN migration.[10] Chemokine analogs like SCH-N, N-(3-AS-CL-HP)-DCPU and N-terminal ELR mutations of CXCL8 have been developed after characterization of the underlying mechanisms of PMN extravasation in pathophysiological conditions. Studies that have employed chemokine analogs in different disease models have been outlined in Table 3. Bovine and human CXCL8 (3-74) K11R/G31P are high-affinity CXCR2 analogs, which blocks the ability of chemokines to activate or attract PMNs *in vitro* or *in vivo*. These analogs significantly antagonize CXCR1 and CXCR2 by inhibiting CXCL8-mediated

Table 2 Summary of studies performed using different CXCR2 antagonists in various experimental models

CXCR2 Blockade	Model	Therapeutic use	Reference
SB225002	Rabbit	Inhibits IL-8-induced PMN recruitment	70
	In vitro	Inhibits IL-8 and GRO-α-induced human and rabbit PMN recruitment	
	Mice	Inhibits PMN migration into intestine in TNBS-induced colitis	71
	Mice	Decreases CXCL1- and N-Ac-PGP-induced PMN inflammation of lungs	40
	In vitro	Inhibits GRO-α-stimulated human PMN migration	72
SB265610 (diaryl urea)	Rats	Decreased hyperoxia-induced PMN accumulation in BAL	39
	In vitro	Blocks CINC-1-induced rat PMN chemotaxis	
SCH527123 (cyanoguanidine compound)	Mice and rats	Inhibits PMN migration into bronchi	50
	Human	Decreases PMN migration into lungs in ozone-induced neutrophilia	73
SB 332235 (Diaryl urea)	Mice	Decreases CXCL1- and N-Ac-PGP-induced PMN inflammation in bronchi and lungs	40
SB455821	Mice	Blocks PMN recruitment into peritoneal cavity	74
	In vitro	Impedes MIP-induced PMN migration	
Nicotinamide *N*-oxides	*In vitro*	Inhibits GRO-α-induced human PMN chemotaxis	45
4 Fluoro nicotinanilides	*In vitro*	Decreases GRO-α-induced human PMN chemotaxis	46
PD0220245, PD 0210293	*In vitro*	Inhibits IL-8-induced human PMN chemotaxis	75
Antileukinate	Mice	Inhibits PMN migration to lungs in bleomycin induced acute lung injury	76
	Rats	Reduces PMN recruitment into lungs in LPS-induced acute lung injury	77
	Rats	Inhibits PMN infiltration into injured spinal cord	78
Reparixin (Repertaxin)	Rats	Inhibits PMN recruitment into cerebrum	79
	In vitro	Inhibits CXCL-1-induced human PMNs	47
	In vitro	Decreases CXCL-1- and CXCL-2-induced rodent PMN chemotaxis	
AZD-8309	Human	Reduces LPS-induced PMN migration in airway inflammation	44
AZ-10397767 (Thiazolopyrimidine compound)	*In vitro*	Inhibits PMN chemotaxis towards CXCL1 and CXCL8	80
		Inhibits TNF-α-stimulated PMN infiltration in to multicellular tumor spheroids	
	Mice	Inhibits PMN migration into xenograft-controlled tumors	
Furanyl cyclobutene diones	*In vitro*	Inhibits GRO-α- and IL-8-induced human PMN migration	81
Acylsufamides	Rats	Inhibits IL-8- and GRO-α-mediated PMN migration in lung injury	82
DF-2162	Rats	Inhibits PMN migration into paws leading to amelioration of adjuvant-induced arthritis	6
	In vitro	Inhibits CXCL8- and CXCL1-induced human PMN migration	48
	In vitro	Reduces CXCL-8- and CXCL1-induced human PMN migration	83
		Reduces CXCL2-induced rat PMN migration	
DF-2156A	Rats	Reduces PMN migration into cerebral ischemia	
SB656933	Human	Inhibits PMN migration into lungs, reduces ozone-induced airway inflammation	84
SB-517785-M (DIARYL UREA)	Rats	Abolishes angiotensin II (Ang II)-induced PMN accumulation into peritoneal cavity	85

CINC-1, cytokine-induced neutrophil chemoattractant 1.

Table 3 Summary of investigations performed in different animal models using various chemokine analogs

Analog	Disease	Model	Therapeutic use	Reference
CXCL8 (3-74) K11R/G31P	LPS-induced lung injury	Guinea pig	Ameliorates acute LPS-induced lung injury by blocking PMN infiltration	86
	LPS-induced endotoxemia	Cattle	Blocks PMN infiltration into intradermal endotoxin challenge sites	54
N-(3-AS-CL-HP)-DCPU	IL-8, LPS, rabbit antigen (OVA) induced arthritis	Rabbit	Inhibits acute and chronic models of arthritis	87
SCH-N	Cigarette smoke-induced lung inflammation	Mice	Inhibits PMN migration into bronchi, and ameliorates lung inflammation	55

OVA, ovalbumin; TNF, tumor necrosis factor.

chemotaxis. It has been shown to inhibit PMN infiltration *in vivo* in LPS-induced inflammation (in cattle) and lung injury (in guinea pig), and *in vitro* in human PMNs.[54] It also reportedly ameliorates artery ischemia reperfusion injury in rats. Recently, a chemokine analog SCH-N has been shown to inhibit PMNs in BAL specimens of cigarette smokers.[55]

CXCR2 antibodies

Prior to discovery of CXCR2 antagonists, various studies have been carried out employing anti-CXCR2 antibodies to demonstrate their role in PMN inflammation and other signalling pathways. Anogen has been developing a topical CXCR2 mAb against psoriasis and has recently been marketed in China. It effectively blocks CXCL8 binding to CXCR2 and eventual migration of PMNs. ABX-IL-8 is another human mAb directed against CXCR2 developed by Xenomouse Technology that acts by neutralizing CXCL8. ABX-IL-8 has recently been shown to improve dyspnea in patients with COPD.[9] However, its clinical development was discontinued in 2002, primarily owing to lack of primary efficacy endpoint against psoriasis and RA.[9] Numerous other antibodies have also been used to block PMN migration in murine models of colitis, lung injury, and infections depicting the importance of CXCR2 in various disease conditions[7,56] (Table 1).

Limitations of blockade of CXCR2

CXCR2 receptor is required for PMN migration, and mediates antimicrobial host defense i.e. killing of pathogens in the body.[35] Blockade of CXCR2 functions in inflammatory diseases involving pathogenic bacteria has resulted in decreased innate immune responses resulting in overwhelming disease, especially in *Streptococcus pneumoniae*,[57] *Pseudomonas aeruginosa*,[58] and *Nocardia asteroides*.[59] Besides, CXCR2 is also involved in vasculogenesis and tumor growth, generation of superoxides in respiratory burst and Ca^{2+} flux in leukocyte subsets.[60,61] Hence, blockade of CXCR2 could also impair other normal functions of CXCR2 culminating in the onset of certain other disorders.

Hetero-oligomerization and characterization of CXCR2 with other receptors such as human DOP opioid have been reported in certain instances.[62] Further, one study suggests that chemokine receptor antagonist can enhance DOP receptor agonist by virtue of its allosteric regulation of heterodimeric partner receptor for CXCR2 receptor.[62] Therefore, utilization of CXCR2 antagonists under different pathologic conditions require assessment of their modes of action and interactions with other receptors,[49] because this might lead to aggravation of other diseases resulting from utilization of the same receptor–ligand interaction.

CXCR1 blockade

Although blockade of CXCR2 is a key to amelioration of inflammatory disorders, CXCR1 blockade also plays a significant role in disease alleviation. Various newer dual CXCR1/CXCR2 inhibitors (as reviewed here), target the allosteric binding sites located on the transmembranes (TM) of the CXCR1/CXCR2 receptors, which noncompetitively inhibit the ligand-binding sites to prevent extravasation of PMNs. Nonetheless, CXCR1 blockade has seldom been studied in small animal models as it is not expressed in rat/mice.

Nanoparticle approach to block CXCR2

Most of the drugs used to inhibit PMN infiltration possess poor oral bioavailability due to certain underlying factors like reduced absorption, rapid renal clearance, and sometimes could lead to toxicity. Because of poor bioavailability, large doses of these drugs need to be administered to produce the desired therapeutic effect. Utility of nanoparticle technology to encapsulate these agents results in numerous salubrious effects, such as increased drug specificity, better efficacy at minimal doses, reduced side-effects and toxicity.[63,64] The different nanoparticle approaches to facilitate the blockade of PMN infiltration in concert with the therapeutic utility of nanodelivery have been summarized in Table 4.

Nanoparticle approach has not yet been used with agents that block CXCR2, which perhaps is a setback in the innovation of these classes of agents. Certain agents

Table 4 Nanoparticles and their use in drugs that block PMN migration in different inflammatory disease models

Drug	Disease	Model	Mechanism of action	Therapeutic use of nanodelivery	Reference
5-amino salicylic acid	IBD	Mice	Blocks production of IL-1, TNF-α	Increases selectivity in drug release aiding in efficient colon targeting	88
Tacrolimus	IBD	Mice	Inhibits lymphocyte signal transduction and IL-2 transcription	Reduces nephrotoxicity	89,90
Rolipram	IBD	Wistar rats	Regulates IL-15 stimulated TNF-α production	Enhances effect of administered dose and reduces side effects	91
Lys-Pro-Val (KPV)	IBD	Mice	Unknown	12,000 times reduction in drug dose with same efficacy	92
Indomethacin	Ocular uveitis, Post-operative inflammation	Rabbit	Regulation of PI3K activation	Increases residence dose, enhances therapeutic index	93

PI3K, phosphatidylinositol 3 kinase; TNF, tumor necrosis factor.

like SB225002, and SCH527123 have shown high-affinity in blocking PMN infiltration, but lacked clinical development due to poor pharmacokinetic profiles, which again is a major setback in the development of such potent drugs. Therefore, application of nanotechnology in this field may open newer frontiers in the development of potent CXCR2 antagonists against inflammatory disorders.

Conclusions

PMN extravasation plays a pivotal role in host defense against various pathogens and diseases. Nonetheless, it is also involved in the pathogenesis of a myriad of other inflammatory disorders. The pathway of PMN migration is a multi-adhesion cascade involving many factors and signalling pathways. Inhibition of PMN and macrophage infiltration has proven to be associated with attenuation of a coterie of inflammatory disorders.[82] However, blockade of CXCR2 may also have deleterious effects, for instance, inhibition of salubrious inflammatory responses, especially under infectious conditions. The inflammatory pathway can be inhibited by various approaches like blockade of chemokine signalling and leukocyte activation by blocking integrins, selectins and transendothelial migration, which has proven to be an effective and novel approach against IBD, RA, pulmonary diseases, and sepsis. Numerous CXCR2 antagonists, antibodies, and chemokine analogs have been developed heretofore, and have proven to be clinically efficient in the treatment of various disorders in animals. Therefore, blockade of CXCR2 appears to be a promising approach opening new frontiers for treating inflammatory disorders, which leads to development of various CXCR2 antagonists as a result of extensive research.

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