



REVIEW

New insights in chemokine signaling [version 1; referees: 3 approved]

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Abstract

Chemokine signaling is essential for coordinated cell migration in health and disease to specifically govern cell positioning in space and time. Typically, chemokines signal through heptahelical, G protein-coupled receptors to orchestrate cell migration. Notably, chemokine receptors are highly dynamic structures and signaling efficiency largely depends on the discrete contact with the ligand. Promiscuity of both chemokines and chemokine receptors, combined with biased signaling and allosteric modulation of receptor activation, guarantees a tightly controlled recruitment and positioning of individual cells within the local environment at a given time. Here, we discuss recent insights in understanding chemokine gradient formation by atypical chemokine receptors and how typical chemokine receptors can transmit distinct signals to translate guidance cues into coordinated cell locomotion in space and time.

Keywords

Chemokine, chemokine receptor, signal transduction, GPCR

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Chemokine-induced signaling

Soon after chemokines were discovered in the late '80s¹⁻³, it was shown that their cognate receptors on cell surfaces were members of the rhodopsin-like family of G protein-coupled receptors (GPCRs). The sensitivity of intracellular signaling to pertussis toxin indicated that the putative receptor for the orphan ligand CXCL8 (formerly interleukin-8[IL-8]) expressed on human neutrophils couples to the G_i class of heterotrimeric proteins⁴. A few years later, the receptors CXCR1 and CXCR2 were identified, cloned, and expressed on mammalian cells for studying signaling properties^{5,6}. Despite their high sequence identity (almost 80%), ligand selectivity is different for the receptors. CXCL8, CXCL5, and CXCL6 bind to both CXCR1 and CXCR2, but the latter also binds the chemokines CXCL1-3 and CXCL7⁷ with high affinity. Hence, chemokines can bind multiple receptors, and on the other side receptors are not always selective for one specific chemokine. Moreover, CXCR1 and CXCR2 differ in their capacity to induce cellular responses upon stimulation with CXCL8. Both receptors stimulate intracellular calcium fluxes, chemotaxis, and degranulation; however, only CXCR1 stimulation leads to activation of phospholipase D and the respiratory burst in human neutrophils^{7,8}. These early observations not only indicated a promiscuity within the chemokine system but also revealed that the GPCRs have the ability to couple differently to downstream signaling pathways. Moreover, a given chemokine can stimulate different responses depending on the receptor to which it binds as well as on the cells where the receptors are expressed.

Typically, chemokine receptor stimulation leads to the GDP/GTP exchange of coupled heterotrimeric G_i proteins and the subsequent dissociation of the βγ subunits, which then activate phosphoinositide-specific phospholipase Cβ (PLC) and phosphoinositide 3-kinase (PI3K). PLC produces inositol-trisphosphate (IP₃) and diacylglycerol (DAG). IP₃ triggers calcium mobilization whereas DAG activates protein kinase C (PKC). PI3K generates 3-phosphoinositides, which serve as anchors in the recruitment of proteins with pleckstrin homology domains to the plasma membrane, such as AKT/PKB⁹. Although these signaling events are common to all chemokine receptors, it is well known that the activation of further downstream pathways is quite different. This may depend on the efficacy with which a chemokine triggers its receptor, giving rise to different spatial and temporal signal fluxes. Such biased signaling at the chemokine receptor was recently revealed by using biosensors to demonstrate differences in G-protein subclass coupling of CCR2, CCR5, and CCR7¹⁰. Other important considerations are the surface expression and density of a receptor and the specific cellular context. As an example, the second ligand of CCR7 CCL19, in contrast to CCL21, does not attract T cells in a microfluidic migration assay under flow conditions¹¹ but does efficiently stimulate migration of cells transfected with the receptor^{12,13}, dendritic cells^{14,15}, or T cells in static migration assays¹⁶. Moreover, monocyte-derived dendritic cells express CCR7 on the cell surface but migrate toward CCL19 and CCL21 only when matured in the presence of prostaglandin E₂^{17,18}. A recent observation indicates that GPCRs move within restricted areas of the cell surface. These

membrane subdomains are maintained by “fences” created by the cytoskeleton and “pickets” made of transmembrane proteins. At special hot spots, GPCRs and G proteins are retained and preferentially couple^{19,20}. These findings imply that signaling by GPCRs can be confined on the cell surface and may depend on the local availability of downstream interaction partners.

Signal bias

Several observations indicate that chemokine receptors may not exclusively couple and signal through G proteins but interact with additional signaling mediators, such as β-arrestins. Upon activation, GPCRs become desensitized through phosphorylation of their intracellular C-termini by second messenger-dependent kinases and GPCR kinases (GRKs). The phosphorylation pattern, also known as barcode, induces arrestin recruitment to the receptor^{21,22}. However, depending on the ligand-mediated stimulation, the recruited β-arrestins cause receptor inactivation and internalization or the receptor-bound arrestin acts as a scaffold which leads to the recruitment and activation of protein kinases²³⁻²⁷. An early definition suggested that agonists which induce receptor internalization are considered G protein-biased but that those which trigger arrestin-dependent signaling are called β-arrestin-biased²². A more complete view of biased signaling takes into account that signal bias can depend on the ligand (ligand bias), the receptor (receptor bias), and the context (tissue bias)^{28,29}. For CXCR4, it was shown that monomeric and dimeric forms of CXCL12, which both may exist under physiological conditions³⁰, induce selective signal transduction pathways and differ in β-arrestin recruitment^{26,27}. Whereas dimeric CXCL12 does not induce β-arrestin recruitment and chemotaxis, both monomeric and dimeric forms of CXCL12 equally trigger the activation of ERK²⁶. For CCR7, CCL19 binding results in robust serine/threonine phosphorylation of the receptor and β-arrestin recruitment catalyzed by GRK3 and GRK6, whereas CCL21 binding activates GRK6 alone³¹. Consequently, CCL19 induces rapid CCR7 internalization whereas CCL21 hardly does³² and hence can be seen as ligand bias¹⁵. Notably, GRK6 contributes to haptotactic sensing of CCL21 gradients at least by dendritic cells³³.

Ogilvie *et al.* showed that CCR2 can activate distinct cellular responses depending on the chemokine which binds to the receptor³⁴. Also, this observation can be seen as ligand bias; however, it does not depend on receptor phosphorylation. Whereas CCL2 induces all typical responses when used to stimulate CCR2, such as calcium fluxes, actin polymerization, and chemotaxis, CCL11 instead was shown in binding assays to act as an antagonist and to suppress CCL2-induced signaling³⁵. More detailed analysis revealed that CCL11 triggered pertussis toxin-sensitive ERK phosphorylation downstream of CCR2 without inducing GDP/GTP exchange of the G protein or leading to receptor phosphorylation. Activation of ERK was required to antagonize CCL2-mediated signaling by CCR2. Both chemokines stimulated PI3K; however, CCL2 stimulated the βγ-dependent PI3Kγ isoform whereas CCL11 activated a p85/p110 isoform³⁴. In general, ligand binding to GPCRs induces the rearrangement of the transmembrane helices³⁶. The above observations

are consistent with a view where CCL2 and CCL11 induce different conformations of CCR2, which translate to diverse intracellular coupling.

Binding of CXCL10 to CXCR3 drives T helper 1 (Th1) polarization via STAT1, 4, and 5 phosphorylation, whereas CXCL11 induces a Th2 and regulatory T (Treg) (IL-10^{hi}) fate involving p70 kinase/mTOR and STAT 3 and 6³⁷. The marked differences in T-cell polarization could be explained by the chemokine-specific signaling. In an early study, which did not investigate T-cell fate, it was shown that the three ligands of CXCR3 (namely CXCL9, CXCL10, and CXCL11) induce typical responses such as calcium mobilization and chemotaxis. By contrast, upon stimulation, CXCR3 internalization was most prominent with CXCL11 whereas CXCL9 and CXCL10 showed only moderate effects. The differences were explained with the use of distinct entities of the intracellular domains of CXCR3 to transmit the responses when stimulated with CXCL9 and CXCL10 versus CXCL11³⁸. More recently, it was shown that CXCL11 and, to a lesser extent, CXCL10, but not CXCL9, induce β -arrestin2 recruitment³⁹. Interestingly, more pronounced differences were reported for β -arrestin recruitment and the binding modality to the two splice variants CXCR3A and CXCR3B, which differ by a 51-amino acid extension at the extracellular N-terminus of CXCR3B^{25,39}. However, expression of the putative CXCR3B in mouse tissue is not clear and this is due to an in-frame stop codon in the coding exon⁴⁰. These observations confirm that intracellular coupling efficiency of the receptor can be modulated by extracellular ligand binding.

Modulation of chemokine receptor signaling

Chemokine activity on cognate receptors can be modulated in multiple ways. The nuclear protein HMGB1, which is released by necrotic or severely stressed cells, binds TLR4 and RAGE but not chemokine receptors. However, HMGB1 forms heterocomplexes with CXCL12, which stimulate CXCR4 with higher potency than the chemokine alone⁴¹. Moreover, chemokines can act synergistically, increasing their potency and efficacy of receptor activation^{42–44}. In addition, chemokine receptors, when triggered with two chemokines, can display allosteric regulation. For example, CXCL14 binds CXCR4 with high affinity but does not stimulate any typical receptor-mediated response. Nevertheless, CXCL14 markedly enhances the potency and efficacy of CXCL12 on CXCR4⁴⁵.

Direct interaction of chemokine receptors with G proteins, GRKs, and β -arrestin is amply reported. In addition, second-messenger kinases, such as PKC and PKA, phosphorylate serine and threonine residues at the C-termini of chemokine receptors. However, some chemokine receptors were shown to directly bind and activate additional proteins, giving rise to receptor-specific activation of signal transduction. CXCR4 interacts with the eukaryotic translation initiation factor eIF2B, suggesting that the receptor may stimulate local protein synthesis⁴⁶. Indeed, mesenchymal cells were shown to *de novo* synthesize actin in the cell periphery^{47,48}. CCR7, when oligomerized, is able to bind and activate an Src kinase signaling pathway which leads to tyrosine phosphorylation within its DRY motif, which then serves as

a docking site for SH2 domain-containing molecules such as phosphatase SHP2⁴⁹. Similarly, the kinase JAK2 was shown to phosphorylate CCR2B upon stimulation with CCL2⁵⁰. Another direct interaction is the binding of VASP to CXCR2 necessary to mediate CXCL8-stimulated cell migration⁵¹. The interaction of FROUNT with CCR2 and CCR5 enhances migration of monocytes and macrophages by increasing consolidated pseudopodium formation^{52,53}.

Chemokine presentation

The chemokine system is well known to orchestrate leukocyte migration through the formation of chemotactic gradients. It should be noted that such chemotactic gradients are locally confined, not exceeding 100–150 μ m⁵⁴. Local confinement implies that chemokines are retained on cell surfaces and the extracellular matrix⁵⁵. Glycosaminoglycan (GAG) binding sites can be found in all chemokines and were shown to be essential to mediate the binding to proteoglycans. Binding of chemokines to GAGs can modify their activities, enhancing or reducing their potency on cognate receptors^{55,56}. On the other side, GAG binding can increase local chemokine concentrations (for example, in receptor vicinity) and efficiently present the ligands for haptotactic chemokine receptor-mediated migration of cells. Secondary B-cell follicles are characterized by germinal centers (GCs) where B-cell antibody affinity maturation occurs. The GCs are split into the CXCL12-rich dark zone, where B-cell centroblasts proliferate, and the CXCL13-rich light zone, where centrocytes are selected for antigen affinity⁵⁷. Specific stroma cells, the CXCL12-expressing reticulate cells (CRCs), produce CXCL12 in the dark zone⁵⁸, whereas follicular dendritic cells release CXCL13 in the light zone⁵⁹. During affinity maturation, B cells move between the two compartments of the GC, being attracted reciprocally by the two chemokines⁵⁷. In transgenic animals which express CXCL12 lacking GAG binding sites, the dark zone is enlarged and poorly defined, consistent with the notion that CXCL12 needs to be locally retained to maintain the structure of the GC, which is not surrounded by physical borders⁶⁰. Similarly, CXCL13 can bind to GAGs without losing its capability to bind to CXCR5, being able to promote adhesion-dependent cell migration⁶¹. However, additional mechanisms, which attenuate B-cell migration at the periphery of GCs, were shown to be essential for efficient B maturation and GC integrity⁶².

Atypical chemokine receptors

An important consideration for the generation and maintenance of biological gradients was made by Francis Crick, who proposed that, in apposition to a source of a morphogen, a sink must exist in order to prevent the gradient from blurring⁶³. Cells migrating on chemokine gradients scavenge the ligands from the surrounding medium and in this way presumably contribute to gradient maintenance⁶⁴. In addition, the group of atypical chemokine receptors (ACKRs), which share the seven-transmembrane domain topology of conventional chemokine receptors but do not couple to G proteins and fail to induce typical intracellular signaling, act as scavengers targeting chemokines for lysosomal degradation^{65,66}. ACKR4 (formerly CCRL1), a scavenger of the chemokines CCL19, CCL21, and

CCL25, is expressed on the lymphatic endothelium (LECs) of subcapsular sinuses (SCSs) of lymph nodes. In the SCSs, the expression of ACKR4 is asymmetric, being present on LECs forming the ceiling of the SCSs but not on those on the floor facing the interfollicular areas. The asymmetric distribution generates CCL21 gradients pointing from the SCS across the floor LECs into the interfollicular areas⁶⁷. This CCL21 gradient is assumed to be critical for dendritic cell and T-cell emigration from SCSs into the parenchyma of lymph nodes. For ACKR3, a scavenger for the chemokines CXCL11 and CXCL12⁶⁸, it was shown, in zebrafish lateral line primordium as a model, that the migrating cell collectives can self-generate CXCL12 gradients across their length^{69,70}. In humans, ACKR3 is upregulated on B cells at the plasmablast stage, when cells downregulate CXCR5 and exit the GCs⁷¹. Because ACKR3 has about a 10-fold higher affinity for CXCL12 than CXCR4, it was concluded that expression of the scavenger renders the cells less sensitive to CXCL12-mediated retention via CXCR4 in the GCs allowing egress. Indeed, migration of plasmablast toward CXCL12 is markedly reduced but can be rescued upon attenuation of ACKR3⁷¹.

Signaling through the chemokine system not only plays a role in hematopoietic cells but also is present in mesenchymal cells. Chemokine signaling is required during development in the central nervous system^{72–74}. ACKR3 was shown to be critical for the migration of interneurons in mouse brain development. The role of the scavenger appears to lie in the control of the level of CXCL12. In the absence of the scavenger, excess of CXCL12 leads to the downregulation of CXCR4 which causes the attenuation of interneuron migration^{75,76}. The chemokine system also plays a pivotal role in angiogenesis, where chemokines induce cell growth and stimulate the recruitment of endothelial cells⁶⁶. The properties of the chemokine system have been adopted by many neoplasms. Several lines of evidence indicate that metastatic infiltration of distant organs such as

the bone marrow, lung, and liver is mediated by chemokines and their cognate receptors^{77–79}. In a recent study⁸⁰, the infiltrating properties of human diffuse large B-cell lymphomas (DLBCLs) into distant organs in a disseminated mouse xenograft model were tested. While organ infiltration is assumed to depend on CXCR4-mediated migration, expression of ACKR3 appeared to play a critical role. In the absence of the scavenger, the DLBCLs fail to infiltrate the organs. *In vitro* studies suggest that ACKR3 is required to generate local CXCL12 gradients during extravasation⁸⁰.

Conclusions

Although all typical chemokine receptors expressed on leukocyte are able to induce cell migration, the signaling mechanisms downstream of the receptors are not unified. Rather, a complex signaling network composed of biased signaling, promiscuous signaling, and signal specificity paired with chemokine presentation and scavenging contributes to chemokine-stimulated cell migration. Such fine tuning is important to allow specific and efficient migration (for example, during immune responses) to guarantee precise spatiotemporal localization of individual effector cells.

Competing interests

The authors declare that they have no competing interests.

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References

- Walz A, Peveri P, Aschauer H, *et al.*: **Purification and amino acid sequencing of NAF, a novel neutrophil-activating factor produced by monocytes.** *Biochem Biophys Res Commun.* 1987; **149**(2): 755–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Yoshimura T, Matsushima K, Oppenheim JJ, *et al.*: **Neutrophil chemotactic factor produced by lipopolysaccharide (LPS)-stimulated human blood mononuclear leukocytes: partial characterization and separation from interleukin 1 (IL 1).** *J Immunol.* 1987; **139**(3): 788–93.
[PubMed Abstract](#)
- Luster AD, Unkeless JC, Ravetch JV: **Gamma-interferon transcriptionally regulates an early-response gene containing homology to platelet proteins.** *Nature.* 1985; **315**(6021): 672–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Thelen M, Peveri P, Kernen P, *et al.*: **Mechanism of neutrophil activation by NAF, a novel monocyte-derived peptide agonist.** *FASEB J.* 1988; **2**(11): 2702–6.
[PubMed Abstract](#)
- Holmes WE, Lee J, Kuang WJ, *et al.*: **Structure and functional expression of a human interleukin-8 receptor.** *Science.* 1991; **253**(5025): 1278–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Murphy PM, Tiffany HL: **Cloning of complementary DNA encoding a functional human interleukin-8 receptor.** *Science.* 1991; **253**(5025): 1280–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Murphy PM, Baggiolini M, Charo IF, *et al.*: **International union of pharmacology. XXII. Nomenclature for chemokine receptors.** *Pharmacol Rev.* 2000; **52**(1): 145–76.
[PubMed Abstract](#)
- Jones SA, Wolf M, Qin S, *et al.*: **Different functions for the interleukin 8 receptors (IL-8R) of human neutrophil leukocytes: NADPH oxidase and phospholipase D are activated through IL-8R1 but not IL-8R2.** *Proc Natl Acad Sci U S A.* 1996; **93**(13): 6682–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Thelen M: **Dancing to the tune of chemokines.** *Nat Immunol.* 2001; **2**(2): 129–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
-  Corbisier J, Galès C, Huszagh A, *et al.*: **Biased signaling at chemokine receptors.** *J Biol Chem.* 2015; **290**(15): 9542–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Nandagopal S, Wu D, Lin F: **Combinatorial guidance by CCR7 ligands for**



- T lymphocytes migration in co-existing chemokine fields.** *PLoS One*. 2011; 6(3): e18183.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Yoshida R, Nagira M, Kitaura M, *et al.*: **Secondary lymphoid-tissue chemokine is a functional ligand for the CC chemokine receptor CCR7.** *J Biol Chem*. 1998; 273(12): 7118–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Otero C, Eisele PS, Schaeuble K, *et al.*: **Distinct motifs in the chemokine receptor CCR7 regulate signal transduction, receptor trafficking and chemotaxis.** *J Cell Sci*. 2008; 121(Pt 16): 2759–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Ricart BG, John B, Lee D, *et al.*: **Dendritic cells distinguish individual chemokine signals through CCR7 and CXCR4.** *J Immunol*. 2011; 186(1): 53–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Hauser MA, Legler DF: **Common and biased signaling pathways of the chemokine receptor CCR7 elicited by its ligands CCL19 and CCL21 in leukocytes.** *J Leukoc Biol*. 2016; 99(6): 869–82.
[PubMed Abstract](#)
16. Schaeuble K, Hauser MA, Singer E, *et al.*: **Cross-talk between TCR and CCR7 signaling sets a temporal threshold for enhanced T lymphocyte migration.** *J Immunol*. 2011; 187(11): 5645–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Scandella E, Men Y, Legler DF, *et al.*: **CCL19/CCL21-triggered signal transduction and migration of dendritic cells requires prostaglandin E2.** *Blood*. 2004; 103(5): 1595–601.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Legler DF, Krause P, Scandella E, *et al.*: **Prostaglandin E₂ is generally required for human dendritic cell migration and exerts its effect via EP2 and EP4 receptors.** *J Immunol*. 2006; 176(2): 966–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Kusumi A, Shirai YM, Koyama-Honda I, *et al.*: **Hierarchical organization of the plasma membrane: investigations by single-molecule tracking vs. fluorescence correlation spectroscopy.** *FEBS Lett*. 2010; 584(9): 1814–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. **S** Sungkaworn T, Jobin ML, Burnecki K, *et al.*: **Single-molecule imaging reveals receptor-G protein interactions at cell surface hot spots.** *Nature*. 2017; 550(7677): 543–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
21. **F** Nobles KN, Xiao K, Ahn S, *et al.*: **Distinct phosphorylation sites on the β_2 -adrenergic receptor establish a barcode that encodes differential functions of β -arrestin.** *Sci Signal*. 2011; 4(185): ra51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
22. Reiter E, Ahn S, Shukla AK, *et al.*: **Molecular mechanism of β -arrestin-biased agonism at seven-transmembrane receptors.** *Annu Rev Pharmacol Toxicol*. 2012; 52: 179–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Hauser MA, Kindinger I, Laufer JM, *et al.*: **Distinct CCR7 glycosylation pattern shapes receptor signaling and endocytosis to modulate chemotactic responses.** *J Leukoc Biol*. 2016; 99(6): 993–1007.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. **F** Luo J, Busillo JM, Stumm R, *et al.*: **G Protein-Coupled Receptor Kinase 3 and Protein Kinase C Phosphorylate the Distal C-Terminal Tail of the Chemokine Receptor CXCR4 and Mediate Recruitment of β -Arrestin.** *Mol Pharmacol*. 2017; 91(6): 554–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
25. Smith JS, Alagesan P, Desai NK, *et al.*: **C-X-C Motif Chemokine Receptor 3 Splice Variants Differentially Activate Beta-Arrestins to Regulate Downstream Signaling Pathways.** *Mol Pharmacol*. 2017; 92(2): 136–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Ziarek JJ, Kleist AB, London N, *et al.*: **Structural basis for chemokine recognition by a G protein-coupled receptor and implications for receptor activation.** *Sci Signal*. 2017; 10(471): pii: eaah5756.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Drury LJ, Ziarek JJ, Gravel S, *et al.*: **Monomeric and dimeric CXCL12 inhibit metastasis through distinct CXCR4 interactions and signaling pathways.** *Proc Natl Acad Sci U S A*. 2011; 108(43): 17655–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Steen A, Larsen O, Thiele S, *et al.*: **Biased and g protein-independent signaling of chemokine receptors.** *Front Immunol*. 2014; 5: 277.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Karin N, Wildbaum G, Thelen M: **Biased signaling pathways via CXCR3 control the development and function of CD4⁺ T cell subsets.** *J Leukoc Biol*. 2016; 99(6): 857–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Ziarek JJ, Veldkamp CT, Zhang F, *et al.*: **Heparin oligosaccharides inhibit chemokine (CXC motif) ligand 12 (CXCL12) cardioprotection by binding orthogonal to the dimerization interface, promoting oligomerization, and competing with the chemokine (CXC motif) receptor 4 (CXCR4) N terminus.** *J Biol Chem*. 2013; 288(1): 737–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Zidar DA, Violin JD, Whalen EJ, *et al.*: **Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands.** *Proc Natl Acad Sci U S A*. 2009; 106(24): 9649–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Otero C, Groettrup M, Legler DF: **Opposite fate of endocytosed CCR7 and its ligands: recycling versus degradation.** *J Immunol*. 2006; 177(4): 2314–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. **F** Schwarz J, Bierbaum V, Vaahtomeri K, *et al.*: **Dendritic Cells Interpret Haptotactic Chemokine Gradients in a Manner Governed by Signal-to-Noise Ratio and Dependent on GRK6.** *Curr Biol*. 2017; 27(9): 1314–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. Ogilvie P, Thelen S, Moepps B, *et al.*: **Unusual chemokine receptor antagonism involving a mitogen-activated protein kinase pathway.** *J Immunol*. 2004; 172(11): 6715–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Ogilvie P, Bardi G, Clark-Lewis I, *et al.*: **Eotaxin is a natural antagonist for CCR2 and an agonist for CCR5.** *Blood*. 2001; 97(7): 1920–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Schwartz TW, Frimurer TM, Holst B, *et al.*: **Molecular mechanism of 7TM receptor activation—a global toggle switch model.** *Annu Rev Pharmacol Toxicol*. 2006; 46: 481–519.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Zohar Y, Wildbaum G, Novak R, *et al.*: **CXCL11-dependent induction of FOXP3-negative regulatory T cells suppresses autoimmune encephalomyelitis.** *J Clin Invest*. 2014; 124(5): 2009–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Colvin RA, Campanella GS, Sun J, *et al.*: **Intracellular domains of CXCR3 that mediate CXCL9, CXCL10, and CXCL11 function.** *J Biol Chem*. 2004; 279(29): 30219–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Borchiche YA, Sakmar TP: **CXC Chemokine Receptor 3 Alternative Splice Variants Selectively Activate Different Signaling Pathways.** *Mol Pharmacol*. 2016; 90(4): 483–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Campanella GS, Colvin RA, Luster AD: **CXCL10 can inhibit endothelial cell proliferation independently of CXCR3.** *PLoS One*. 2010; 5(9): e12700.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Schiraldi M, Raucci A, Muñoz LM, *et al.*: **HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4.** *J Exp Med*. 2012; 209(3): 551–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Kuscher K, Danelon G, Paoletti S, *et al.*: **Synergy-inducing chemokines enhance CCR2 ligand activities on monocytes.** *Eur J Immunol*. 2009; 39(4): 1118–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Paoletti S, Petkovic V, Sebastiani S, *et al.*: **A rich chemokine environment strongly enhances leukocyte migration and activities.** *Blood*. 2005; 105(9): 3405–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Gouwy M, Struyf S, Noppen S, *et al.*: **Synergy between coproduced CC and CXC chemokines in monocyte chemotaxis through receptor-mediated events.** *Mol Pharmacol*. 2008; 74(2): 485–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
45. Collins PJ, McCully ML, Martínez-Muñoz L, *et al.*: **Epithelial chemokine CXCL14 synergizes with CXCL12 via allosteric modulation of CXCR4.** *FASEB J*. 2017; 31(7): 3084–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. Palmesino E, Apuzzo T, Thelen S, *et al.*: **Association of eukaryotic translation initiation factor eIF2B with fully solubilized CXCR4.** *J Leukoc Biol*. 2016; 99(6): 971–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Kislaukus EH, Zhu X, Singer RH: **Sequences responsible for intracellular localization of beta-actin messenger RNA also affect cell phenotype.** *J Cell Biol*. 1994; 127(2): 441–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. **F** Hüttelmaier S, Zenklusen D, Lederer M, *et al.*: **Spatial regulation of beta-actin translation by Src-dependent phosphorylation of ZBP1.** *Nature*. 2005; 438(7067): 512–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
49. Hauser MA, Schaeuble K, Kindinger I, *et al.*: **Inflammation-Induced CCR7 Oligomers Form Scaffolds to Integrate Distinct Signaling Pathways for Efficient Cell Migration.** *Immunity*. 2016; 44(1): 59–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
50. Mellado M, Rodríguez-Frade JM, Aragay A, *et al.*: **The chemokine monocyte chemotactic protein 1 triggers Janus kinase 2 activation and tyrosine phosphorylation of the CCR2B receptor.** *J Immunol*. 1998; 161(2): 805–13.
[PubMed Abstract](#)
51. Neel NF, Barzik M, Raman D, *et al.*: **VASP is a CXCR2-interacting protein that regulates CXCR2-mediated polarization and chemotaxis.** *J Cell Sci*. 2009; 122(Pt 11): 1882–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
52. Toda E, Terashima Y, Sato T, *et al.*: **FROUNT is a common regulator of CCR2 and CCR5 signaling to control directional migration.** *J Immunol*. 2009; 183(10): 6387–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. **F** Terashima Y, Onai N, Murai M, *et al.*: **Pivotal function for cytoplasmic protein FROUNT in CCR2-mediated monocyte chemotaxis.** *Nat Immunol*. 2005; 6(8): 827–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

54. **F** Weber M, Hauschild R, Schwarz J, *et al.*: **Interstitial dendritic cell guidance by haptotactic chemokine gradients.** *Science*. 2013; **339**(6117): 328–32. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
55. **F** Proudfoot AEI, Johnson Z, Bonvin P, *et al.*: **Glycosaminoglycan Interactions with Chemokines Add Complexity to a Complex System.** *Pharmaceuticals (Basel)*. 2017; **10**(3): pii: E70. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Proost P, Struyf S, van Damme J, *et al.*: **Chemokine isoforms and processing in inflammation and immunity.** *J Autoimmun*. 2017; **85**: 45–57. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. Victora GD, Nussenzweig MC: **Germinal centers.** *Annu Rev Immunol*. 2012; **30**: 429–57. [PubMed Abstract](#) | [Publisher Full Text](#)
58. **F** Rodda LB, Bannard O, Ludewig B, *et al.*: **Phenotypic and Morphological Properties of Germinal Center Dark Zone *Cxcl12*-Expressing Reticular Cells.** *J Immunol*. 2015; **195**(10): 4781–91. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. **F** Wang X, Cho B, Suzuki K, *et al.*: **Follicular dendritic cells help establish follicle identity and promote B cell retention in germinal centers.** *J Exp Med*. 2011; **208**(12): 2497–510. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
60. **F** Barinov A, Luo L, Gasse P, *et al.*: **Essential role of immobilized chemokine CXCL12 in the regulation of the humoral immune response.** *Proc Natl Acad Sci U S A*. 2017; **114**(9): 2319–24. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
61. **F** Monneau YR, Luo L, Sankaranarayanan NV, *et al.*: **Solution structure of CXCL13 and heparan sulfate binding show that GAG binding site and cellular signalling rely on distinct domains.** *Open Biol*. 2017; **7**(10): pii: 170133. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
62. **F** Muppidi JR, Lu E, Cyster JG: **The G protein-coupled receptor P2RY8 and follicular dendritic cells promote germinal center confinement of B cells, whereas S1PR3 can contribute to their dissemination.** *J Exp Med*. 2015; **212**(13): 2213–22. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
63. Crick F: **Diffusion in embryogenesis.** *Nature*. 1970; **225**(5231): 420–2. [PubMed Abstract](#) | [Publisher Full Text](#)
64. Volpe S, Cameroni E, Moepps B, *et al.*: **CCR2 acts as scavenger for CCL2 during monocyte chemotaxis.** *PLoS One*. 2012; **7**(5): e37208. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. Bachelier F, Graham GJ, Locati M, *et al.*: **New nomenclature for atypical chemokine receptors.** *Nat Immunol*. 2014; **15**(3): 207–8. [PubMed Abstract](#) | [Publisher Full Text](#)
66. Bachelier F, Ben-Baruch A, Burkhardt AM, *et al.*: **International Union of Basic and Clinical Pharmacology. [corrected]. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors.** *Pharmacol Rev*. 2014; **66**(1): 1–79. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. **F** Ulvmar MH, Werth K, Braun A, *et al.*: **The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes.** *Nat Immunol*. 2014; **15**(7): 623–30. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. Naumann U, Cameroni E, Pruenster M, *et al.*: **CXCR7 functions as a scavenger for CXCL12 and CXCL11.** *PLoS One*. 2010; **5**(2): e9175. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. **F** Donà E, Barry JD, Valentin G, *et al.*: **Directional tissue migration through a self-generated chemokine gradient.** *Nature*. 2013; **503**(7475): 285–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
70. Venkiteswaran G, Lewellis SW, Wang J, *et al.*: **Generation and dynamics of an endogenous, self-generated signaling gradient across a migrating tissue.** *Cell*. 2013; **155**(3): 674–87. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Humpert ML, Pinto D, Jarrossay D, *et al.*: **CXCR7 influences the migration of B cells during maturation.** *Eur J Immunol*. 2014; **44**(3): 694–705. [PubMed Abstract](#) | [Publisher Full Text](#)
72. Nagasawa T, Nakajima T, Tachibana K, *et al.*: **Molecular cloning and characterization of a murine pre-B-cell growth-stimulating factor/stromal cell-derived factor 1 receptor, a murine homolog of the human immunodeficiency virus 1 entry coreceptor fusin.** *Proc Natl Acad Sci U S A*. 1996; **93**(25): 14726–9. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Nagasawa T, Hirota S, Tachibana K, *et al.*: **Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1.** *Nature*. 1996; **382**(6592): 635–8. [PubMed Abstract](#) | [Publisher Full Text](#)
74. Ma Q, Jones D, Borghesani PR, *et al.*: **Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice.** *Proc Natl Acad Sci U S A*. 1998; **95**(16): 9448–53. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. **F** Sánchez-Alcañiz JA, Haeghe S, Mueller W, *et al.*: **Cxcr7 controls neuronal migration by regulating chemokine responsiveness.** *Neuron*. 2011; **69**(1): 77–90. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
76. Abe P, Mueller W, Schütz D, *et al.*: **CXCR7 prevents excessive CXCL12-mediated downregulation of CXCR4 in migrating cortical interneurons.** *Development*. 2014; **141**(9): 1857–63. [PubMed Abstract](#) | [Publisher Full Text](#)
77. **F** Caronni N, Savino B, Recordati C, *et al.*: **Cancer and Chemokines.** *Methods Mol Biol*. 2016; **1393**: 87–96. [PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. Massara M, Bonavita O, Mantovani A, *et al.*: **Atypical chemokine receptors in cancer: friends or foes?** *J Leukoc Biol*. 2016; **99**(6): 927–33. [PubMed Abstract](#) | [Publisher Full Text](#)
79. Balkwill FR: **The chemokine system and cancer.** *J Pathol*. 2012; **226**(2): 148–57. [PubMed Abstract](#) | [Publisher Full Text](#)
80. Puddinu V, Casella S, Radice E, *et al.*: **ACKR3 expression on diffuse large B cell lymphoma is required for tumor spreading and tissue infiltration.** *Oncotarget*. 2017; **8**(49): 85068–84. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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