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An atypical addition to the chemokine receptor nomenclature: IUPHAR Review 15

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Chemokines and their receptors are essential regulators of *in vivo* leukocyte migration and, some years ago, a systematic nomenclature system was developed for the chemokine receptor family. Chemokine receptor biology and biochemistry was recently extensively reviewed. In this review, we also highlighted a new component to the nomenclature system that incorporates receptors previously known as 'scavenging', or 'decoy', chemokine receptors on the basis of their lack of classical signalling responses to ligand binding and their general ability to scavenge, or sequester, their cognate chemokine ligands. These molecules are now collectively referred to as 'atypical chemokine receptors', or ACKRs, and play fundamental roles in regulating *in vivo* responses to chemokines. This commentary highlights this new addition to the chemokine receptor nomenclature system and provides brief information on the four receptors currently covered by this nomenclature.

Abbreviation

ACKR, atypical chemokine receptor

This article, written by members of the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) subcommittee for the chemokine receptors, confirms the existing nomenclature for these receptors and reviews our current understanding of their structure, pharmacology and functions and their likely physiological roles in health and disease. More information on this receptor family can be found in the Concise Guide to PHARMACOLOGY <http://onlinelibrary.wiley.com/doi/10.1111/bph.12445/abstract> and for each member of the family in the corresponding database http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=14.
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These tables list protein targets and ligands that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and the Concise Guide to PHARMACOLOGY2013/14 (Alexander *et al.*, 2013a,b).

Introduction

Chemokines are the principal regulators of *in vivo* leukocyte migration and membership of the chemokine family is defined by the presence of variations on a conserved cysteine motif within the mature proteins (Rot and von Andrian, 2004). This family is further divided into four subfamilies (CC, CXC, XC and CX3C) according to the specific nature of this cysteine motif. Chemokine regulation of leukocyte migration is complicated but chemokines can be broadly characterized as being either inflammatory, or homeostatic, according to the contexts in which they function (Mantovani, 1999; Zlotnik and Yoshie, 2000). Thus, inflammatory chemokines regulate the migration of leukocytes to infected, inflamed or wounded tissue sites, while homeostatic chemokines are involved in the basal trafficking of leukocytes into, and out of, peripheral tissues and secondary lymphoid organs. In addition to controlling leukocyte migration, the chemokine family displays a significant element of pleiotropy with particular roles being seen in the regulation of stem cell migration both during embryogenesis, as well as in the adult. Indeed, this is likely to have been the primordial role for chemokines (Nomiyama *et al.*, 2011). This notion is supported by the fact that chemokines are a vertebrate 'invention' (Zlotnik *et al.*, 2006; Nomiyama *et al.*, 2011) and one of the most ancient chemokines, CXCL12, is essential for the proper migration of haemopoietic stem cells to the bone marrow both late in development and in the adult (Lapidot and Petit, 2002; Lapidot *et al.*, 2005). CXCL12 is also responsible for the migration of primordial germ cells to the genital ridge during development (Doitsidou *et al.*, 2002; Ara *et al.*, 2003) as well as for the migration of a number of other key developmental cell types. From this single gene and its defined biological role, the family has expanded through gene duplication to the point where mammals now have approximately 45 chemokines (Zlotnik *et al.*, 2006) that are involved, in sometimes very complex and subtle ways, in regulating immune and inflammatory cell migration.

Regardless of their individual function, chemokines interact with 7-transmembrane spanning receptors (Alexander *et al.*, 2013a,b and http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=14), which are typically, but not exclusively, coupled to G-proteins for signalling (Bachelerie *et al.*, 2014). Currently, there are 10 receptors identified for CC chemokines, 7 for CXC chemokines and single receptors for the XC and CX3C chemokines. Again, chemokine receptors can be broadly classified as being inflammatory or homeostatic according to their function. A characteristic of chemokine receptors involved in inflammation is that they tend to be highly promiscuous and can bind numerous inflammatory chemokines with high affinity. Further complicating this is the fact that many inflammatory chemokines are able to bind to numerous inflammatory chemokine receptors. This, coupled with emerging evidence of 'biased signalling' through chemokine receptors (Zweemer *et al.*, 2014), highlights the complexity of the orchestration of inflammatory responses. We currently have a limited understanding of chemokine involvement in inflammation and this is a major disadvantage in terms of therapeutically targeting chemokine receptors in inflammatory, and autoimmune, pathologies (Schall and Proudfoot, 2011).

Atypical chemokine receptors and the new nomenclature

In addition to the classical signalling chemokine receptors, there exists a subfamily of receptors referred to as 'atypical chemokine receptors' that are characterized by either an apparent inability to signal, or the use of alternative signalling pathways to those seen with the classical receptors (Graham *et al.*, 2012; Nibbs and Graham, 2013). Specifically, while the classical chemokine receptors typically couple to G-proteins for signalling, the atypical receptors are unable to couple to G-proteins and, where signalling can be demonstrated, they have been shown to preferentially mediate β-arrestin-based responses to ligand binding. (Nibbs and Graham, 2013). A further characteristic of the atypical receptors is an altered DRYLAIV motif in the second intracellular loop and this alteration explains, in part, the lack of G-protein coupling by these receptors. The peculiarities in the signalling responses, driven by the atypical receptors, have meant that their pharmacological properties have largely been defined on the basis of ligand-binding assays with chemokines typically binding in the low nM range.

There are currently four members of the atypical chemokine receptor family (Table 1), which are described below, and these molecules are involved in the fine-tuning, or resolution, of chemokine-based responses in both homeostatic and inflammatory contexts. This receptor family has, until recently, been on the 'fringes' of chemokine biology; however, a number of observations now attest to the fundamental biological roles played by these molecules in a variety of *in vivo* situations. This receptor subfamily is therefore achieving significant prominence, and accordingly, we felt it appropriate to develop a systematic nomenclature for its members. The agreed nomenclature system involves naming these receptors as ACKRs (atypical chemokine receptors) and numbering them in the order that they were first reported as being atypical chemokine binders. The members of the atypical chemokine receptor subfamily have recently been extensively reviewed (Graham *et al.*, 2012; Nibbs and Graham, 2013; Bachelerie *et al.*, 2014) and so only brief details are provided here. The four currently accepted members of the ACKR family are the following:

(i) ACKR1 [formerly known as the Duffy Antigen Receptor for Chemokines, or DARC (Novitzky-Basso and Rot, 2012)]. ACKR1 was characterized as being the cell surface molecule supporting red blood cell invasion by the malarial parasites *Plasmodium vivax* and *knowlesi*. ACKR1 is highly expressed on red blood cells, and subsets of vascular endothelial cells, and expression is also seen on neurons. ACKR1 is unique among vertebrate chemokine receptors in that it can bind, with high affinity, both CC and CXC chemokines. The chemokines bound by ACKR1 are all involved in inflammatory responses and ACKR1 has been shown to be important for ligand transcytosis across endothelial layers, to ensure presentation in the vascular lumen, as well as in buffering inflammatory chemokine levels in the circulation. In contrast to the other atypical receptors mentioned below, ACKR1 is not believed to possess ligand-scavenging activity (Pruenster *et al.*, 2009). In terms of the evolutionary relationship to the other classical and atypical chemokine receptors, ACKR1 is a slight 'outlier' in that its primary sequence and chromosomal localization suggest that it may not have evolved from within the chromosomal loci encoding the signalling chemokine receptors (Nomiyama *et al.*, 2011). There are currently no data to support ACKR1 signalling in response to ligand binding.

(ii) ACKR2 [formerly known as D6 or ccbp2 (Graham and Locati, 2013)]. ACKR2 is a broad specificity receptor for inflammatory CC chemokines that is expressed predominantly by lymphatic endothelial cells but also by some leukocyte subsets, most notably innate-like B cells. ACKR2 is also inducibly expressed by keratinocytes and is a prominent feature of human psoriatic skin. Another major site of ACKR2 expression is the syncytiotrophoblast layer in the placenta. ACKR2 mounts non-classical, β-arrestin-dependent, signalling responses to ligand binding (Borroni *et al.*, 2013) but, most importantly, this molecule internalizes the chemokines that it binds and targets them for intracellular degradation. This has led to it being characterized as a scavenging receptor for inflammatory CC chemokines. This function allows it to control the resolution of inflammatory responses, as well as other aspects of peri-lymphatic leukocyte migration.

Table 1

The basic properties of the ACKRs

Name	Alternative names	Ligands	Demonstrated signalling mechanisms	Sites of expression
ACKR1	DARC, CD234, Duffy antigen	CCL1,2,5,7,8,11,13,14,16,17,18 CXCL1,2,3,4,5,6,8,9,10,11,13	None defined	Red blood cells, vascular endothelial cells, Purkinje cells.
ACKR2	Ccbp2, D6, CMKBR9	CCL2,3,3L1,4,5,6,7,8,11,12,13, 14,17,22,23,24,26	β-arrestin	Lymphatic endothelial cells, B1 B cells, trophoblastic cells, keratinocytes.
ACKR3	RDC1, CXCR7, CMKOR1	CXCL11, 12. Adrenomedullin, opioid peptides	β-arrestin	Vascular endothelial cells, haematopoietic cells, neurons, various developmental cell types.
ACKR4	CCRL1, CCXCKR, CCR11	CCL19, 21, 25. CXCL13	β-arrestin	Lymphatic endothelial cells, germinal centre B cells, thymic epithelial cells.

Mice deficient in ACKR2 have problems resolving inflammatory responses and difficulty in maintaining pregnancy in the presence of systemic maternal inflammation. The gene-encoding ACKR2 is incorporated within one of the major chromosomal loci incorporating other chemokine receptors, and thus, ACKR2 is evolutionarily related to these other receptors (Nomiyama *et al.*, 2011).

(iii) ACKR3 [formerly known as RDC1 or CXCR7 (Sánchez-Martín *et al.*, 2013)]. ACKR3 binds CXCL11 and CXCL12 and is expressed by a variety of cell types. There are clear roles for ACKR3 in regulating vascular, cardiac and brain development and numerous cancer cells, and cancer-associated blood vessels, express this receptor. There have been some extremely elegant studies into roles for ACKR3 during development where it fine-tunes CXCR4-dependent cellular migration and contributes to CXCL12-dependent aspects of embryonic patterning. Similar to ACKR2, signalling studies indicate that ACKR3 mediates β-arrestin-dependent responses and is capable of internalizing and degrading ligands, and thus, again, is active as a chemokine-scavenging molecule. A peculiarity of ACKR3 is its additional ability to scavenge chemokine-unrelated proteins. Initially described as a receptor for adrenomedullin (Kapas *et al.*, 1995), it was recently shown that ACKR3-mediated scavenging of adrenomedullin is critical for the growth of lymphatic vessels (Klein *et al.*, 2014). Finally, ACKR3 is also able to bind opioid peptides and thus directly contribute to the modulation of circadian glucocorticoid oscillation (Ikeda *et al.*, 2013). The gene encoding ACKR3 is incorporated within one of the major chromosomal loci encoding other chemokine receptors, from which it is clearly evolutionarily derived (Nomiyama *et al.*, 2011). It is important to point out that, due to common prior usage, CXCR7 will be retained as an alias for ACKR3 and this designation will, therefore, not be available for any other CXC chemokine receptors.

(iv) ACKR4 [formerly known as CCRL1 or CCXCKR (Hansell *et al.*, 2006)]. ACKR4 binds the homeostatic CC chemokines CCL19, 21 and 25 and displays a very limited expression profile being seen predominantly on thymic epithelial cells, keratinocytes and lymphatic endothelial cells lining the ceiling of the subcapsular sinus of lymph nodes. ACKR4 is able to internalize and degrade its ligands and thus acts as a scavenging receptor for these homeostatic CC chemokines. Recent data suggest important roles for this molecule in regulating dendritic cell entry into the lymph node parenchyma (Ulvmar *et al.*, 2014). The gene encoding ACKR4 is incorporated within one of the chromosomal loci including other chemokine receptors from which it has therefore clearly evolved (Nomiyama *et al.*, 2011).

Concluding comments

In summary, therefore, the systematic nomenclature system for chemokine receptors has been broadened to incorporate four atypical chemokine receptors. The ACKRs have distinct signalling properties, and play fundamental roles in patterning chemokine-based responses *in vivo*. They are, therefore, essential contributors to the overall orchestration of chemokine activity in developmental, immune and inflammatory contexts. This new nomenclature system will further expand as other atypical chemokine receptors are reported. Indeed, ACKR5 and ACKR6 designations are currently being reserved pending confirmation of chemokine binding by CCRL2 (Leick *et al.*, 2010) and PITPNM3 (Chen *et al.*, 2011) respectively.

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Conflict of interest

The authors declare no conflicts of interest regarding this manuscript and its contents.

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