The FEBS Journal

FEBS PRESS science publishing by scientists

A GUIDE TO...

A guide to chemokines and their receptors

Catherine E. Hughes and Robert J. B. Nibbs

Institute of Infection, Inflammation & Immunity, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK

Keywords
atypical chemokine receptor; cell migration; chemokine; chemokine receptor; glycosaminoglycan; immune surveillance; inflammation; leukocyte; oligomerization; protease

Correspondence
R. J. B. Nibbs, Sir Graeme Davies Building, 120 University Place, Glasgow, G12 8TA Scotland, UK
Fax: +44 141 330 4297
Tel: +44 141 330 3960
E-mail: robert.nibbs@glasgow.ac.uk

(Received 26 January 2018, revised 25 March 2018, accepted 3 April 2018)

doi:10.1111/febs.14466

The chemokines (or chemotactic cytokines) are a large family of small, secreted proteins that signal through cell surface G protein-coupled heptahelical chemokine receptors. They are best known for their ability to stimulate the migration of cells, most notably white blood cells (leukocytes). Consequently, chemokines play a central role in the development and homeostasis of the immune system, and are involved in all protective or destructive immune and inflammatory responses. Classically viewed as inducers of directed chemotactic migration, it is now clear that chemokines can stimulate a variety of other types of directed and undirected migratory behavior, such as haptotaxis, chemokinesis, and haptokinesis, in addition to inducing cell arrest or adhesion. However, chemokine receptors on leukocytes can do more than just direct migration, and these molecules can also be expressed on, and regulate the biology of, many nonleukocytic cell types. Chemokines are profoundly affected by post-translational modification, by interaction with the extracellular matrix (ECM), and by binding to heptahelical 'atypical' chemokine receptors that regulate chemokine localization and abundance. This guide gives a broad overview of the chemokine and chemokine receptor families; summarizes the complex physical interactions that occur in the chemokine network; and, using specific examples, discusses general principles of chemokine function, focusing particularly on their ability to direct leukocyte migration.

Chemokines

Chemokines are defined by their primary amino acid sequence and the arrangement of specific structurally important cysteine residues within the mature protein. These form disulfide bonds that maintain the structure of the chemokine monomer, which consists of a central three stranded β-sheet, an overlying C-terminal α-helix, and a short unstructured N terminus that plays a critical role in receptor activation [1]. Variation in the precise configuration of the two cysteines closest to the N terminus allows chemokines to be split into four

Abbreviations
ACKR, atypical chemokine receptor; ADM, adrenomedullin; ADRA1A/B, α1A/B-adrenoreceptors; BM, bone marrow; C-18, cyclophilin-18 of *T. gondii*; CB2, cannabinoid receptor 2; cCKR, conventional chemokine receptor; CCL, CC chemokine ligand; CCR, CC chemokine receptor; CNS, central nervous system; CX_3CL, CX_3C chemokine ligand; CX_3CR, CX_3C chemokine receptor; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor; DBP, Duffy binding protein; DC, dendritic cell; DOR, delta-opioid receptor; ECM, extracellular matrix; FPRL1, formyl peptide receptor-like 1; GAG, glycosaminoglycan; GluR1, component of the AMPA-type glutamate receptor; Glyco G, RSV G glycoprotein; gp120, envelope protein of HIV; GPCR, G protein-coupled receptor; GPR75, G protein-coupled receptor 75; HIV, human immunodeficiency virus; HlgAB, *Staphylococcus aureus* γ-Hemolysin AB; HMGB1, high mobility group box 1 protein; HSC, hematopoietic stem cell; KOR, kappa-opioid receptor; LEC, lymphatic endothelial cell; LTi, lymphoid tissue inducer; LukED, *Staphylococcus aureus* leukotoxin ED; MIF, macrophage migration inhibitory factor; MMP, matrix metalloproteinase; MOR, mu-opioid receptor; PITPMN3, phosphatidylinositol transfer protein 3; PSMB, PC3-secreted microprotein; RSV, respiratory syncytial virus; TCR, T-cell receptor; Treg, regulatory T cell; TSG-6, TNF-stimulated gene 6; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; XCL, XC chemokine ligand; XCR, XC chemokine receptor; β2AR, β2-adrenergic receptor.

subfamilies: CC, CXC, CX_3C, and XC. In CC chemokines, these cysteines are directly juxtaposed, while CXC chemokines have a single variable amino acid between them. The sole CX_3C chemokine has three amino acids between these two cysteines, while XC chemokines, of which there are two forms in humans and one in mice, lack the first and the third cysteines of the motif. Large numbers of CC and CXC chemokine genes have been defined in many species (Fig. 1) [2]: not all are found in all species, or sometimes all members of a species; nonallelic isoforms exist, such as *CCL3L1* and *CCL3* in humans [3,4] and *Ccl21a*, *Ccl21b*, and *Ccl21c* in mice [5]; and allelic and copy number variation creates considerable genetic diversity that influences susceptibility to, and severity of, a number of diseases [3,6,7].

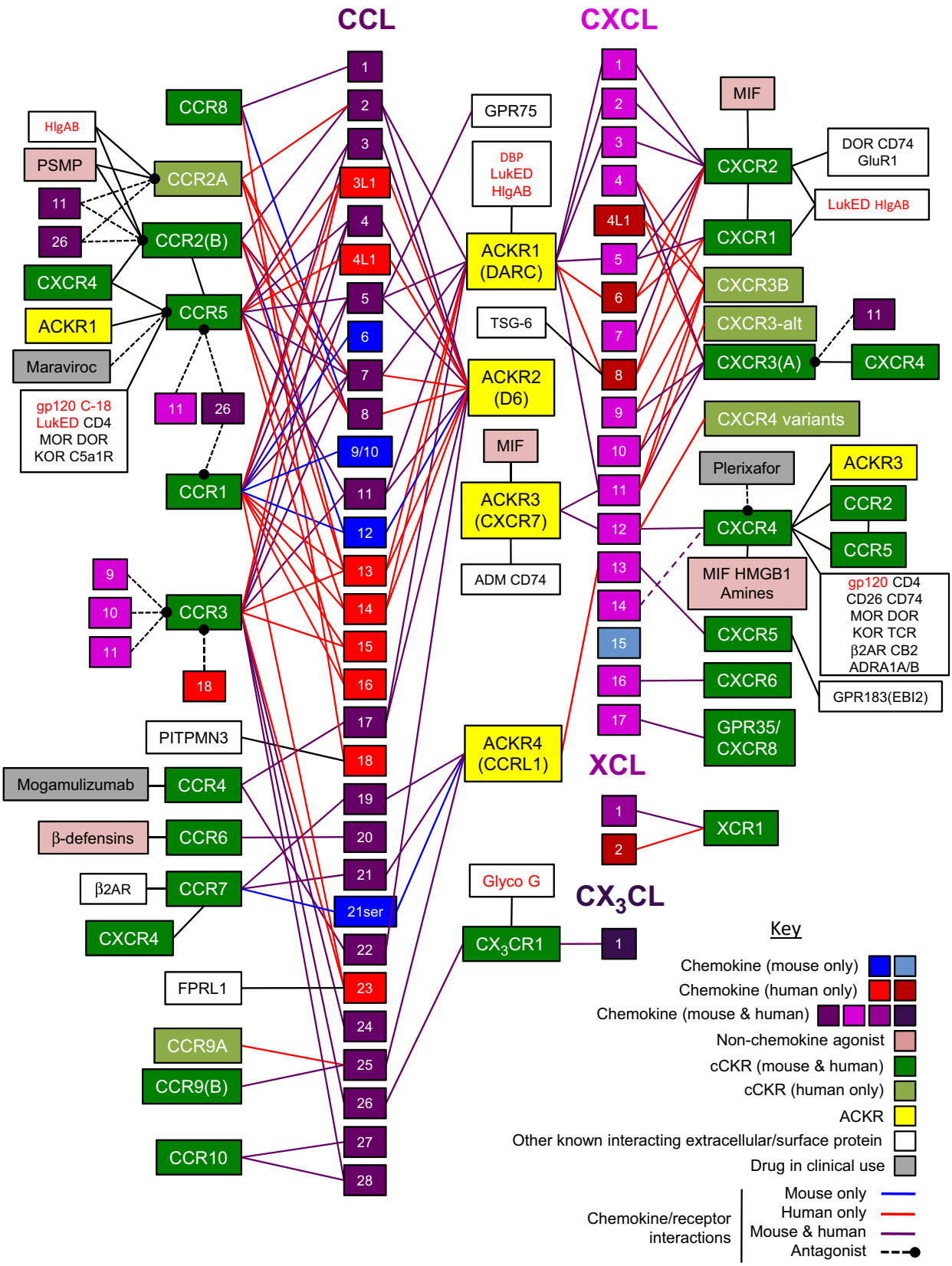
Although chemokines were originally named according to specific functions, a systematic nomenclature was introduced in 2000 that includes a subfamily designation (i.e., CC, CXC, CX_3C, or XC), followed by the letter L (denoting 'ligand'), and then a number according to when the gene was first isolated [8,9]. Chemokines with the same name from different species are often functional orthologues [2], although this is not always the case: for example, human CCL8 binds to the human CCR2 receptor, while mouse CCL8 is a CCR8 ligand [10], and mouse CCL3 is functionally more like human CCL3L1 than human CCL3 [11]. All chemokines are produced with an N-terminal signal peptide that is removed once it has directed the chemokine into the endoplasmic reticulum for secretion. Two chemokines, CX_3CL1 and CXCL16, have an extended C terminus containing a mucin-like stalk and a transmembrane domain [12,13]. This holds these chemokines on the cell surface but can be proteolytically cleaved to release the chemokine portion into the extracellular space [14–18]. Other chemokines, such as CCL6, CCL9, and CCL23, have an extended N terminus that can be proteolytically removed to enhance receptor activation capabilities [19]. An N-terminal peptide cleaved off a CCL23 variant can activate formyl peptide receptor-like 1 (FPRL1), a G protein-coupled receptor (GPCR) not classified as a cCKR [20]. Alternatively spliced transcripts can generate chemokine variants: for example, six forms of human CXCL12 have been described with different C termini [21] and distinct biological properties [22,23].

GAGs, oligomerization, and post-translational modification

The postsecretion activity and distribution of chemokines depends on how readily they become immobilized on cell surfaces and ECM [24,25]. Glycosaminoglycans (GAGs) are particularly important in this regard. Their ability to bind chemokines influences chemokine/receptor interactions; chemokine half-life in a tissue or tissue compartment; how, and where, a chemokine operates *in vivo*; and the type of cell movement or adhesion it stimulates [24,25]. They are essential for maintaining interstitial chemokine functions and gradients [26–28] and for the presentation of chemokines on endothelial surfaces, preventing them being washed away by the blood and so allowing them to drive leukocyte arrest and extravasation [29–31]. Some chemokines, such as CCL21, are very 'sticky' and become rapidly immobilized, while others, such as CCL19, which activates the same receptor as CCL21, likely diffuse more readily through tissues [27]. In addition, mammalian proteins, including TSG-6, can interfere with chemokine/GAG interactions to alter chemokine distribution and function [32,33]. Targeted disruption of chemokine/GAG interactions might have therapeutic impact [34], as could GAG-based chemokine-capturing hydrogels [35].

While chemokines are active as monomers, they also form homodimers, heterodimers, and higher order aggregates that can contain one or more chemokine species, and this can be influenced by interactions with GAGs [36–40]. The full chemokine 'interactome' reveals complex and extensive interactions: human CXCL4 and CCL5, for example, can each heterodimerize/oligomerize with over 20 other chemokines from CC, CXC, and XC subfamilies [40]. The structures formed rely on two types of interfaces, referred to as CC- and CXC-type, in which chemokine activity is typically enhanced and inhibited, respectively [40]. Oligomerization clearly influences how individual or mixtures of chemokines combine to control leukocyte responses, and disrupting specific interactions may have therapeutic potential [1,25,39–41].

Chemokines are also profoundly affected by post-translational modifications such as citrullination [42–44], nitration/nitrosylation [45–47], and cleavage by matrix metalloproteinases (MMPs), cathepsins, thrombin, plasmin, elastase, the dipeptidyl peptidase CD26, and other proteases [48–50]. These changes can substantially modify chemokine activity. For example, nitration of tyrosine residues in CCL2 by reactive nitrogen species reduces the ability of this chemokine to attract monocytes through its receptor CCR2 [45], while arginine residues in a number of chemokines can be converted into citrulline by the enzyme peptidylarginine deiminase: this reduces the chemotactic activity of CXCL8, CXCL10, and CXCL11, and prevents conversion of CXCL8 into a more active shortened



form by interfering with thrombin- and plasmin-mediated N-terminal trimming [42,44].

Proteases are key chemokine regulators. CD26-mediated trimming of two amino acids off a chemokine's N terminus can, depending on the chemokine, change receptor specificity, substantially alter receptor affinity or convert agonists into antagonists [48]. Many MMPs can also modify this part of certain chemokines, and the impact of these modifications depends on the identity of the chemokine being studied. Thus, MMP-mediated N-terminal trimming typically enhances the activity of CXCR2 ligands, and of CC chemokines with extended N-termini (CCL6, CCL9, CCL23), while CXCL12 is inactivated by MMPs and CCR2 ligands are converted into receptor antagonists [50]. Proteolytic cleavage of the C terminus of chemokines can dramatically alter ECM binding properties and diffusivity. For example, DC-mediated cleavage of CCL21 removes the highly charged C terminus that anchors it to the ECM, thereby releasing a version of this key DC attractant that has much higher diffusivity than the full-length protein [51]. This is rather similar to the release of CX_3CL1 and CXCL16 from cell surfaces that was mentioned above [14–18]. MMPs and other proteases can also act on the C terminus of chemokines: for example, MMP processing of the C terminus of CCL16 enhances its GAG-binding properties [52]. Proteases are also thought to help create and modify interstitial chemokine gradients, and have the capacity to degrade chemokines, or the ECM to which they are bound, so are important in regulating chemokine half-life and distribution [49,53]. Controlling protease regulation of chemokines could have therapeutic application: for example, inhibiting CD26-mediated cleavage of CXCL10 enhances tumor immunotherapy in mouse models [54].

Chemokine receptors

There are two families of heptahelical surface molecules that bind to chemokines: conventional chemokine receptors (cCKRs) and atypical chemokine receptors (ACKRs) (Fig. 1).

Conventional chemokine receptors

Chemokine-bound cCKRs typically transduce signals through pertussis toxin-sensitive $G\alpha_i$ G-proteins and β-arrestins, ultimately leading to cell migration, adhesion and/or a variety of other biological responses. Chemokines are thought to initially tether to their cognate cCKR via the extracellular loops and N terminus of the receptor: the negative charge on these cCKR domains can be increased by glycosylation, polysialylation, and/or the incorporation of sulphated tyrosine residues. Sulphated tyrosines in the N terminus aid HIV gp120 binding to CCR5 [55] and enhance chemokine binding to CCR2 [56], CCR3 [57], CCR5 [55,58],

Fig. 1. Mammalian chemokine receptors and their known interactions with chemokines and other key secreted, cell surface, and pathogen-encoded molecules. Chemokines of the four subclasses (CCL, CXCL, CX_3CL, and XCL) are arranged numerically in columns and represented as numbered squares that are color-coded according to whether they are in humans and mice, humans only, or mice only (see Key). The chemokine–chemokine 'interactome' [40] is not depicted. Chemokines are linked by lines to receptors that they are known to bind: yellow boxes are atypical chemokine receptors (ACKRs) (previous names shown in parentheses); green boxes are conventional chemokine receptors (cCKRs); and light green boxes show reported human cCKR variants generated by alternative splicing at the N terminus (CCR9, CXCR3, CXCR4) or C terminus (CCR2) [69–74]. The color of the linking line (see Key) indicates whether the interaction likely exists in humans only, mice only, or in humans and mice. Hashed black lines ending with a filled circle link chemokines with receptors they can antagonize [119–126]. CXCL14 is reported to be a positive allosteric modulator of CXCR4 [344]. Chemokine receptors reported to form heterodimers are linked with a black line [93–101,118]. Nonchemokine proteins in light pink boxes are able to activate the cCKR they are joined to by a black line [89–92,102,347]. White boxes contain microbial proteins (red text) and other host extracellular/surface proteins (black text; nonchemokine, nonchemokine receptor) that have been reported to interact, in the absence of chemokine, with the cCKR or ACKR to which they are attached by a black line [32,92,102–117,147–152,167,233,264,345–348]. Note that cCKRs and ACKRs other than those shown are known to be capable of binding HIV and/or gp120, but the role of these chemokine receptors during infection is uncertain. CCL18 receptor PITPMN3 and CCL5 receptor GPR75 are also shown [127,348]. FPRL1 interacts with a peptide released proteolytically from the N terminus of one form of CCL23 [20]. Gray boxes show drugs in clinical use: Maraviroc [143] and Plerixafor [237], antagonists of CCR5 and CXCR4, respectively; and Mogamulizumab, a humanized anti-CCR4 antibody approved for treatment of relapsed or refractory CCR4+ adult T-cell leukemia/lymphoma (CTCL) [349]. Definitions: ADM, adrenomedullin; ADRA1A/B, α1A/B-adrenoreceptors; C-18, cyclophilin-18 of *Toxoplasma gondii;* CB2, cannabinoid receptor 2; DBP, Duffy binding protein of malarial parasites *P. vivax* and *P knowlesi;* DOR, delta-opioid receptor; GluR1, component of the AMPA-type glutamate receptor; Glyco G, RSV G glycoprotein; gp120, the gp120 envelope protein of HIV; GPR75, G protein-coupled receptor 75; HlgAB, *Staphylococcus aureus* γ-Hemolysin AB; HMGB1, high mobility group box 1 protein; KOR, kappa-opioid receptor; LukED, *S. aureus* leukotoxin ED; MIF, macrophage migration inhibitory factor; MOR, mu-opioid receptor; PITPMN3, phosphatidylinositol transfer protein 3; PSMP, PC3-secreted microprotein; TCR, T-cell receptor; TSG-6, TNF-stimulated gene 6; β2AR, β2-adrenergic receptor. Extended from previous reviews [64,350].

CCR8 [59], CXCR3 [60], CXCR4 [61], and CX_3CR1 [62]. Polysialylation of CCR7 is essential for its activation by CCL21, appearing to release CCL21 from an auto-inhibited conformation [63].

Once a chemokine is tethered to a cCKR, its unstructured N terminus enters the cCKR's heptahelical bundle to induce a conformational change that is translated into intracellular signals [64,65]. This classical two-site model of chemokine/receptor interaction is probably oversimplistic, with recent studies suggesting that the two supposedly independent ligand-binding sites can be physically and allosterically linked, and that additional interactions between chemokine and receptor are likely to be involved in ensuring full receptor activation [64]. The signaling pathways downstream of chemokine receptors are complex, and a detailed description is beyond the scope of this review, but they include, among others, heterotrimeric G-proteins, β-arrestins, and JAK-STAT pathways [66,67].

There are currently 18 cCKRs named according to the predominant type of chemokine they bind (i.e., CC, CXC, CX_3C, or XC), followed by the letter R (denoting 'receptor'), and then a number reflecting the order of their discovery (green boxes, Fig. 1). There are 10 CCRs, 6 CXCRs, and a single CX_3CR and XCR. GPR35 has recently been identified as a CXCL17 receptor and referred to as CXCR8 [68], but may become known as CXCR7 now that the original CXCR7 has been renamed ACKR3 [66]. Transcripts encoding cCKRs can be subject to alternative splicing: variants of CCR2, CCR9, CXCR3, and CXCR4 have been reported with altered ligand-binding or signaling properties [69–74]. Important detailed insights into cCKR structure, chemokine binding, and mechanisms of antagonism have come with the resolution of crystal structures of CCR2, CCR5 CCR9, CXCR4, and US28, a cytomegalovirus-encoded chemokine receptor, and from other biophysical approaches [64,65,75–84].

Receptor specificity is complex: many chemokines bind to multiple cCKRs, and some cCKRs have many ligands (Fig. 1). This is prominent among chemokines/cCKRs involved in inflammation, while those primarily involved in homeostatic cell migration have only one or two ligands that are faithful to a single cCKR. Chemokines vary with respect to their affinity for a particular cCKR, and biased signaling, or functional selectivity, is emerging as a key feature of cCKRs, such that the precise pathways activated by a cCKR depend on which ligand it binds, and the cellular context of that binding [85–88]. Currently, six cCKRs have been reported to show biased signaling [88]. Moreover, some cCKRs can also be activated by non-chemokine ligands: β-defensins can activate CCR6 [89]; the 'alarmin' high mobility group box 1 protein (HMGB1) is emerging as a key CXCR4 ligand [90,91]; and cells expressing CXCR2 or CXCR4 migrate in response to macrophage migration inhibitory factor (MIF) (light pink boxes, Fig. 1) [92].

Like other GPCRs, cCKRs exist as homodimers. They can also aggregate into higher order oligomers, and form functionally distinct heterodimers with ACKRs, other cCKRs, nonchemokine-binding GPCRs (such as opioid receptors), and other membrane proteins (white boxes, Fig. 1) [87,93–118]. Some chemokines can act as natural cCKR antagonists (Fig. 1) [119–126]. Phosphatidylinositol transfer protein (PITPMN3), a non-GPCR with six transmembrane domains, is reported to be a functional receptor for CCL18 in the context of tumor cell invasion [127], although, more conventionally, CCL18 also binds to, and directs leukocyte migration through, the cCKR CCR8 [128].

The striking receptor/ligand promiscuity common in the chemokine network most likely evolved to combat microbial subversion by building robustness into leukocyte responses during infection. Many viral genomes carry genes encoding chemokines, chemokine-binding proteins, and/or heptahelical receptors capable of interfering with parts of the host chemokine system; or they contain genes encoding chemokines and/or chemokine receptors that activate, or are activated by, host cCKRs or chemokines [129]. The saliva of blood-sucking ticks contains chemokine-binding proteins thought to suppress inflammation at the bite site [130–132]. Human immunodeficiency virus (HIV) has evolved to exploit cCKRs: CXCR4, and particularly CCR5, are vital coreceptors mediating HIV entry into cells and can dock to the HIV gp120 envelope protein after it has bound CD4 [133–139]. The ligands for these cCKRs block HIV entry into cells by steric hindrance or cCKR down-regulation, and genetic variation in genes encoding CXCL12, CCR5, and CCR5 ligands profoundly influences susceptibility to HIV infection and the rate of progression to AIDS [3,7,140]. Most notably, homozygosity for the non-functional Δ32-*CCR5* allele profoundly protects against HIV infection, while Δ32-*CCR5* heterozygosity is associated with slowed progression to AIDS in most cohorts of HIV-infected people [7,140–142]. CCR5 antagonist Maraviroc [143] is now used clinically, alongside other drugs, to delay progression to AIDS in HIV-positive patients, and there was considerable publicity when transplantation of HLA-matched stem cells from Δ32-*CCR5* homozygotes proved very effective in treating an HIV-infected patient [144]. However, some caution is required because after infection with West

Nile Virus, Δ32-*CCR5* homozygosity increases the likelihood of developing encephalitic symptoms, and of dying from the infection [145], most likely due to defects in the trafficking of protective leukocytes into the brain [146].

Other pathogens target chemokine receptors. Some malarial parasites use ACKR1 to enter erythrocytes (see below); cyclophilin-18 from *Toxoplasma gondii* binds to, and signals through, CCR5 [147]; respiratory syncytial virus (RSV) uses it's glycoprotein G to infect a subset of B cells through CX_3CR1 [148]; and *Staphylococcus aureus* leukotoxin ED (LukED) and γ-hemolysin AB toxin (HlgAB) target ACKR1 and various cCKRs to lyse erythrocytes and kill leukocytes, respectively [149–152]. These interactions have important consequences for the pathogenicity of these microorganisms.

Atypical chemokine receptors

Atypical chemokine receptors, of which there are four (yellow boxes, Fig. 1), are structurally related to cCKRs but do not couple to many, if any, of the signal transduction pathways activated by cCKRs [66,153]. Many publications report signaling and associated biological responses via ACKR3, but it remains unclear and/or controversial whether ACKR1, 2, and 4 can transduce signals at all after chemokine binding [154]. This may be in part due to the absence, or modification, of appropriate signaling motifs on the intracellular surface of ACKRs, such as the canonical DRYLAIV motif present in the second intracellular loop of cCKRs [153]. However, ACKRs bind chemokines with high affinity [154], and, like cCKRs, use sulphated tyrosine residues to enhance chemokine binding [155,156].

All ACKRs appear to be involved in regulating chemokine localization, distribution, and abundance, thereby indirectly controlling interactions between chemokines and cCKRs [153]. For example, ACKR1 transports chemokines across endothelial cells for presentation to blood-borne leukocytes [157,158], and, on erythrocytes, ACKR1 buffers chemokine abundance in the blood [159–163]: this likely prevents cCKRs on circulating leukocytes being inappropriately desensitized by exposure to excess chemokine. Interestingly, ACKR1 can regulate hemopoietic stem and progenitor cells in the bone marrow (BM), and control neutrophil phenotype/abundance in the blood, although the underpinning molecular mechanisms remain unclear [164,165]. ACKR1 is pirated by malarial parasites *Plasmodium vivax* and *Plasmodium knowlesi*, which use their Duffy binding protein (DBP) to engage ACKR1 and gain entry into erythrocytes [166–168]. Genetic variation in *ACKR1* profoundly influences susceptibility to infection by these parasites, and the complete loss of ACKR1 from erythrocytes is very common in sub-Saharan African populations [169,170]. The absence of ACKR1 from erythrocytes also appears to cause benign ethnic neutropenia [165,171,172] and may influence HIV infection by leading to CCR5 ligand dysregulation or loss of ACKR1-mediated HIV presentation [173,174], although this was not borne out in other studies [175–178].

ACKR2 is a well-characterized chemokine scavenger. It constitutively shuttles to and from cell surfaces without needing chemokine-induced signals to do so, and internalizes any chemokines it encounters while exposed to the extracellular space [179,180]. Internalized chemokine is dislodged from ACKR2 and degraded [179,180]. ACKR2 serves key regulatory functions in developing mammary gland and on lymphatic endothelial cells (LECs), innate-like B cells, and placental trophoblasts [181–190]. ACKR3 is instrumental in controlling the CXCL12-CXCR4 axis, either by scavenging CXCL12 or by heterodimerizing with, and regulating the function of, CXCR4 [99,100,191–200]. ACKR4-mediated scavenging of CCL19 and/or CCL21 can regulate CCR7-dependent dendritic cell migration and adaptive immune responses [201–204], and roles for this ACKR have been reported in the thymus [205,206]. cCKRs can also remove extracellular chemokines, albeit less efficiently than ACKRs, and internalization of surface chemokine/cCKR complexes is a key aspect of cCKR regulation. Consequently, mice in which a cCKR gene has been deleted can have elevated levels of the chemokine(s) that normally bind that cCKR [207]. Thus, chemokine regulation by receptor-mediated internalization is not limited to ACKRs.

The function of the chemokine network

By far the most studied function of the chemokine network is cell migration, particularly of leukocytes. However, the biological activity of chemokines is by no means limited to this function or to these cell types (Fig. 2). As recently reviewed elsewhere [208], a wide variety of other biological processes can be induced by the activation of cCKRs on leukocytes, including proliferation, survival, differentiation, cytokine production, degranulation, and respiratory burst (Fig. 2). Moreover, several chemokines have direct antimicrobial activity [209]. In addition, many nonleukocytic cell types, including neurons, astrocytes, epithelial cells, mesenchymal cells, and endothelial cells, can express

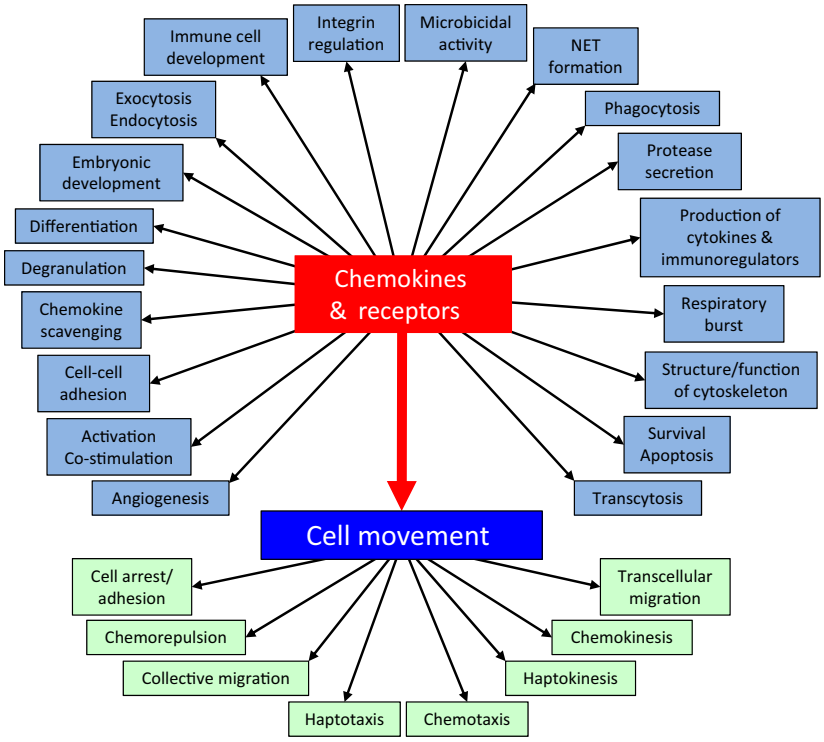


Fig. 2. Functions of chemokines and their receptors. Biological processes reported to be regulated by chemokines and their receptors are in light blue boxes arranged clockwise, in alphabetical order (starting bottom left), around the central 'Chemokines & Receptors' box. 'Cell Movement' is depicted as the dominant biological process regulated by chemokines and their receptors: chemokine-mediated cell arrest/adhesion, and the different types of migratory behavior known to fall under chemokine control, are shown in light green boxes.

cCKRs and respond in a wide variety of ways to chemokines [210–216]. For example, many chemokines directly regulate angiogenesis, with distinct subsets showing negative or positive angiogenic activity [214,215]. Interestingly, cancer cells of nonleukocytic origin can evolve to express cCKRs and respond to chemokines: this can encourage local invasion, spread to draining lymph nodes, and the metastatic seeding of distant tissues [217,218]. Cell movement is the dominant biological process regulated by chemokines and their receptors, and many different types of cell movement that have been reported fall under chemokine control, including chemotaxis (often seen as the classic chemokine-driven form of migration) and also encompassing haptotaxis, chemokinesis, haptokinesis and transcellular migration. In some contexts, chemokines can direct the migration of groups of cells (referred to as collective migration) [219–221], or stimulate cell adhesion, causing cell movement to stop. There are also reports of cells moving down, rather than up, chemokine concentration gradients, i.e., away from the chemokine source, a process termed chemorepulsion or chemofugetaxis [222–224] (Fig. 2).

Leukocyte migration is of critical immunological importance. Leukocytes must be in the right place at the right time so that their immunological functions can be appropriately localized and directed. Immune surveillance requires the continuous trafficking of leukocytes out of BM and into, within, and out of the other tissues of the body. When tissues become damaged and/or infected, the rapid recruitment of innate immune cells is essential to kill pathogens, prevent microbial dissemination, drive inflammation, and help repair damage. The elaboration of a regulated adaptive immune response, and the subsequent development of immune memory, depends on further carefully choreographed leukocyte migratory processes. Chemokines are of central importance in all these processes driving leukocytes into and out of blood and lymphatic vessels, and directing their interstitial movement and positioning. Without chemokine-directed leukocyte migration, immune tolerance breaks down, immunosurveillance fails, and protective immune responses are compromised. However, chemokine-directed leukocyte migration also contributes to diseases that have an immune or inflammatory component including autoimmunity, allergy, chronic inflammatory disease, atherosclerosis, cancer, and many others. In this context, interfering with chemokine-directed leukocyte migration has therapeutic potential.

The size of the chemokine and cCKR families enables leukocyte recruitment to be tailored to fit the immunological needs of tissues. While many molecules are required for cells to be able to leave the bloodstream and navigate within tissues [29,225], typically the expression of a particular cCKR enables a

leukocyte to migrate in response to that receptor's ligands. Figure 3 shows the expression of chemokine receptor genes in a variety of leukocytes and stromal cells in mice. These data are consistent with protein expression data, and broadly conserved in humans. Some cCKR genes, such as *Ccr3*, *Cxcr1*, and *Cxcr2*, clearly show highly restricted patterns of expression, while others, particularly *Cxcr4*, are more uniformly expressed. ACKRs are mainly limited to stromal cells, although *Ackr1* is expressed by erythrocyte precursors (not shown in Fig. 3) [164] and the other ACKRs are transcribed in discrete subsets of B cells [99,189,226].

Leukocyte activation can change cCKR expression profiles dramatically to couple changes in immunological function with switches in migratory potential. This makes sense if the new function requires the cell to localize to a different tissue or microanatomical niche. This is discussed below in the context of CD4+ T cells. Likewise, distinct tissues or tissue domains express specific profiles of chemokines under homeostatic conditions (Fig. 4), and this changes with infection or damage when the immunological requirements of the tissue change. For example, in mice, CCL25 is constitutively expressed in the small intestine [227], while mouse skin makes substantial quantities of CXCL14, CCL8 ,and CCL27 [10,228,229], but when these or other tissues are damaged, inflamed or infected, large numbers of inflammatory chemokines are induced to direct the rapid recruitment of innate immune cells and the subsequent homing of effector T cells.

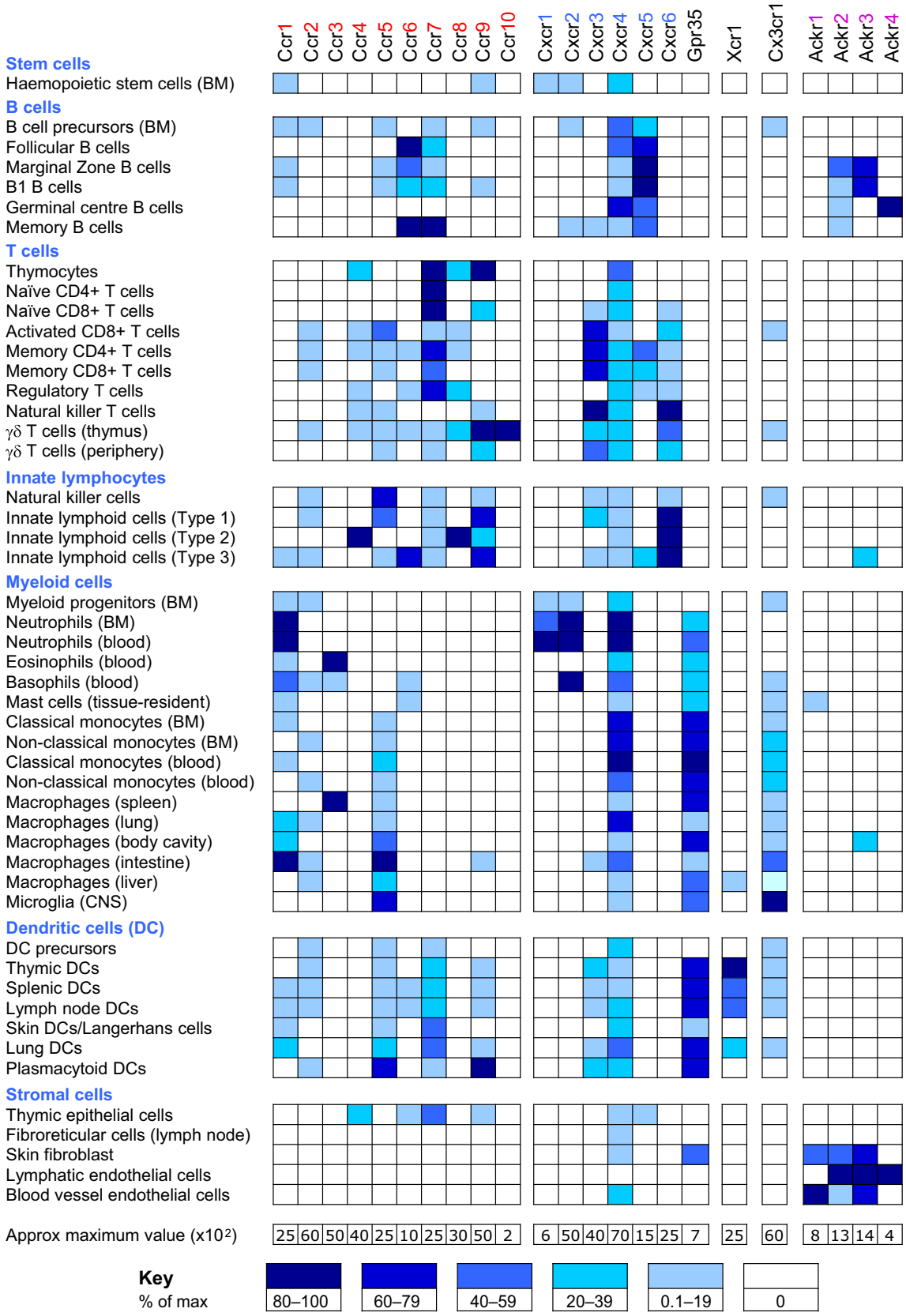
Development, homeostasis, and immune surveillance

Only the CXCL12/CXCR4/ACKR3 node of the chemokine network is necessary for life. CXCL12, the most primitive chemokine, has been strongly conserved through evolution. Acting through CXCR4 and regulated by ACKR3, CXCL12 is critical for the development of the heart, brain, vascular system, hematopoietic system, germ cells, and, in fish, the lateral line [99,191–200,230–232]. Deletion of *Cxcl12* or *Cxcr4* in mice results in a variety of developmental abnormalities and death *in utero* [230–232]. *Ackr3* deficiency has a similar outcome, although some *Ackr3*-deficient mice survive until birth [99,193,194]. ACKR3-mediated scavenging of adrenomedullin (ADM) may be significant during heart and lymphatic vasculature development [233]. Many indispensable functions for CXCL12 have been defined in the adult, including its role in hematopoiesis where it is a key component of the niche that supports hematopoietic stem cells (HSCs) in the BM [234–236]. Blocking CXCR4 function liberates HSCs from the BM, and CXCR4 antagonist AMD3100 (Plerixafor) is used clinically to mobilize HSCs for collection from peripheral blood prior to autologous stem cell transplantation [237].

Autosomal dominant mutations in CXCR4 are responsible for WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency, myelokathexis syndrome), a rare genetic disease in which patients have IgG antibody deficiency, neutropenia (due to retention of neutrophils in the BM), and increased susceptibility to bacterial and viral infections (including human papillomaviruses, which causes warts) [238]. The mutations truncate or mutate the C terminus of CXCR4 [238,239], disrupting negative regulatory domains and enhancing receptor activity [240,241]. Plerixafor shows promise as a therapeutic [242] and there is a remarkable report that chromothripsis, a process in which chromosomes undergo extensive rearrangements and deletions, spontaneously cured a WHIM syndrome patient [243].

CXCR5 and CCR7 serve key developmental roles by regulating the homing of lymphoid tissue inducer (LTi) cells. During embryonic life, these cells migrate out of the blood into sites where secondary lymphoid tissues will form. This is critical for the development of lymph nodes and Peyer's patches, and mice defective in both the CXCR5/CXCL13 and CCR7/CCL21 axes lack Peyer's patches and virtually all lymph nodes [244–249].

Some cCKRs serve well-defined homeostatic tissue-specific functions driven by the constitutive expression of their ligands under steady-state conditions (Fig. 4). For example, several chemokine receptors, including CCR4, CCR9, and particularly CCR7, contribute to T-cell development by enabling cells to enter and navigate within the thymus [250–260]. This facilitates the selection and differentiation processes that are essential for central tolerance, the generation of the naïve T-cell repertoire, and natural regulatory T-cell (nTreg) formation. Deletion of *Ccr7* or its ligands disrupts thymocyte trafficking in mice creating an aberrant naïve T-cell repertoire that drives autoimmunity [252–255,261]. CCR7 is also essential for leukocyte entry into lymph nodes and other secondary lymphoid tissues [262], with recent reports describing circadian fluctuations in the CCL21/CCR7 axis and lymphocyte trafficking into lymph nodes controlled by adrenergic nerves [263–265]. CCR7 facilitates lymphocyte recruitment from blood [266]; stimulates intranodal T-cell motility [267–269] and retention [264,270]; directs dendritic cells (DCs) [27] and other leukocytes [271,272] into tissue lymphatic vessels along CCL21 gradients [27] aided by DC-induced



CCL21 secretion from LECs [273]; mediates intralymphatic crawling [274,275]; and allows DCs to enter the lymph node parenchyma from the subcapsular sinus [276]. Thus, in addition to directing central tolerance, CCR7 is essential for peripheral tolerance and the initiation of adaptive immune responses [262].

There are many other instances of chemokine-driven homeostatic leukocyte trafficking. For example, CCR2 is required for Ly6C^{hi} monocyte release from BM [277]; CCR3 controls steady-state eosinophil distribution [278]; CXCR2 and CXCR4 direct neutrophil egress from, and return to, the BM [279,280]; monocytes use CX_3CR1 to patrol blood vessel walls [281]; and CCR9 regulates plasmacytoid DC and intraepithelial γδ T-cell abundance in the small intestine [258,282]. B cells are specifically directed to lymphoid tissue follicles by CXCR5 [244,245], which also controls marginal zone B cell and B1 B cell migration in mouse spleen and body cavities, respectively [283,284].

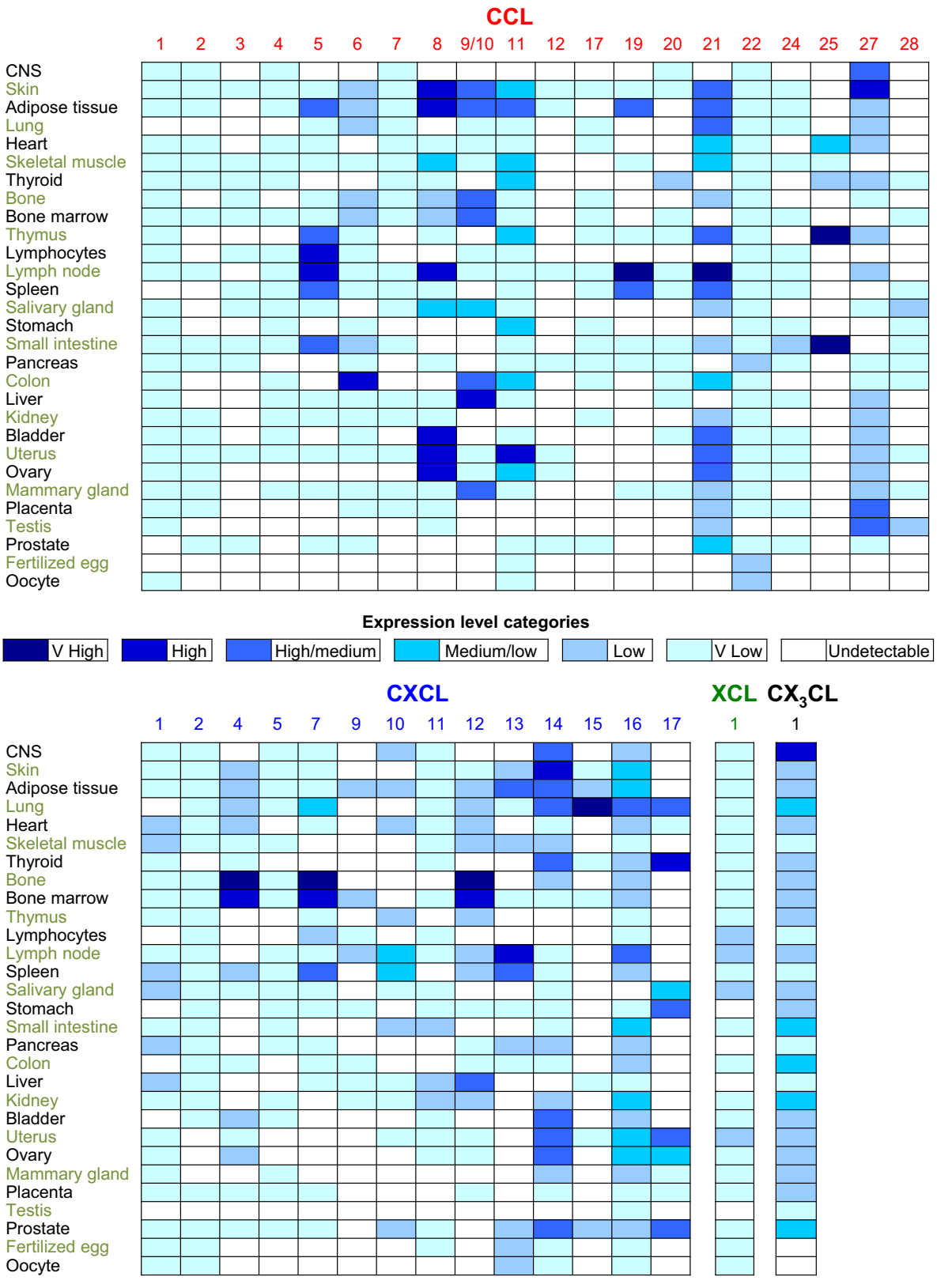
Therefore, chemokine-driven cell migration serves critical developmental functions; ensures immunological tolerance is established and maintained; enables antigen-specific lymphocytes to enter and survey antigen-presenting cells in lymphoid tissue; and distributes leukocytes around the body so they are appropriately placed to respond to immunological challenge.

Infection, inflammation, and immunopathology

Chemokines, along with an array of other proteins, peptides, lipids, and microbial products, direct leukocyte recruitment into infected or damaged tissues [66,285]. Many chemokines are highly inducible and produced in large quantities in response to a broad array of infectious and inflammatory stimuli. Leukocytes recruited by chemokines early to damaged or infected tissues can produce other chemokines that contribute to the next wave of leukocyte homing [286,287]. Chemokines are produced by many diseased tissues, including those affected by autoimmunity [288–290], allergy [291], Alzheimer's disease [292], chronic inflammatory disease [293], cardiovascular disease [294], and cancer [295]. These inflammatory chemokine profiles typically include those chemokines that bind to the promiscuous cCKRs and ACKRs (i.e., CCR1, CCR2, CCR3, CCR5, CXCR1, CXCR2, CXCR3, ACKR1, and ACKR2) (Fig. 1), but other chemokines can also be induced, and the precise chemokine profile in a given tissue will depend on the exact nature of the inducing stimuli, the phase of the response, and the genetics of the chemokine network in the affected individual.

Inflammatory chemokine abundance, distribution, and activity will be controlled by their interactions with ECM, proteases, and other proteins within the tissue, and by scavenging via cCKRs and ACKRs, particularly ACKR1 and ACKR2. Inflammatory chemokines make a major contribution to the recruitment of leukocyte populations required to meet the immunological needs of affected tissues, and will regulate any nonleukocyte tissue cells (epithelial, mesenchymal, and/or endothelial) constitutively or inducibly expressing cCKRs. Many microbes have evolved to interfere with inflammatory chemokines and cCKRs, leading to an 'arms race' that has built robustness and redundancy into this part of the chemokine network. Nonetheless, individual cCKRs serve indispensable roles in a variety of contexts, and there is a vast literature describing how deleting, inhibiting, or blocking individual cCKRs or ACKRs impacts on a wide variety of experimentally induced immune and inflammatory responses, and modifies pathology in a diverse array of animal models of human disease. This understandably led to the development of small molecule cCKR antagonists to trial in patients with immune or inflammatory disease [66]. However, despite considerable efforts, to our knowledge, no effective therapeutics for these diseases have yet emerged, and while the in-built robustness of the inflammatory chemokine network has no doubt been a contributing factor, several other likely reasons have been proposed and discussed [296]. Nonetheless, clinical trials using chemokine receptor antagonists, or other therapeutic approaches that target or exploit chemokines, continue to take place.

Fig. 3. Expression of chemokine receptor genes in selected mouse leukocytes and stromal cells. The figure was generated using transcriptomic data from The Immunological Genome Project database (www.immgen.org) [351]. The maximum expression value was identified for the cell types shown and is indicated in the row at the bottom of the Figure in arbitrary units. For each receptor, this value was set to 100%. Estimated background values (typically between 50 and 100) were determined by examining expression graphs for all cell types on the database. Expression in the cell types shown in the left hand column was then assigned a color according to the percentage of the maximum expression value (see Key on right). Note that not all cells in a cell population will necessarily express the receptor. BM, bone marrow; DC, dendritic cell.



Chemokine receptor switching

Changes in leukocyte function are intimately associated with switches in cCKR expression. For example, DC trafficking from tissues to draining lymph nodes requires inflammatory cCKRs to be lost and CCR7 to be switched on [262,297–299]. cCKR switching is also prominent during CD4+ and CD8+ T-cell activation and differentiation, and cCKRs are reported to directly contribute to T-cell costimulation [300,301]. When CD4+ T cells encounter antigen, they can differentiate into one of many functionally distinct T cell types, including effector T cells (Th1, Th2, and Th17), follicular T cells (Tfh and Tfr), induced regulatory T cells (iTreg), and memory T cells (Tcm and Tem). These cells have discrete immunological functions that require specific migratory behaviors so they need to express particular cCKR profiles. Th1 cells typically express CCR5 and CXCR3 (as do many recently-activated CD8+ T cells); Th2 cells preferentially display CCR3 and CCR4; and Th17 are often CCR6+ [302–308]. This enables these effector T cells to home to infected or inflamed tissues where they contribute to microbial clearance and tissue repair. In contrast, Tfh and Tfr cells control activated B cells so need to enter B cell follicles in lymphoid tissues: they achieve this by up-regulating CXCR5 expression [309–314]. Likewise, during viral infection, CXCR5 is expressed by some activated cytotoxic T cells so that they enter follicles to attack virally infected Tfh and B cells [315].

Antigen-experienced T cells can be imprinted with cCKRs that enable them to selectively home to specific tissues. T cells that encounter antigen in mesenteric lymph nodes draining the small intestine will often express CCR9 to enable homing back to the small intestine [316–319]. This depends on the specialization of DC and stromal cells in the mesenteric lymph nodes and production of retinoic acid from dietary vitamin A [319–324]. Likewise, T cells activated in skin-draining lymph nodes typically express CCR4, CCR8, or CCR10 to enable homing to the skin: this may depend on skin-derived vitamin D_3 and keratinocyte products [10,229,325–329]. In contrast, central memory CD4+ and CD8+ T cells (Tcm), like naïve T cells, traffic through secondary lymphoid organs using CCR7, while other memory T cells lose CCR7 and express cCKRs that enable them to home to nonlymphoid tissues [330]. These memory cells can remain resident in the nonlymphoid tissue or home back to lymph nodes by up-regulating CCR7 [271,272]. In addition, recent work has defined three functionally distinct subsets of antigen-experienced CD8+ T cells based on their differential expression of CX_3CR1 [331].

Antigen-experienced B cells also use chemokine receptor switching to direct differentiated cells to discrete tissues or tissue domains. CCR7 up-regulation directs activated B cells to the boundary of the follicle and the T-cell area [332]. CXCR4 and CXCR5 are involved in the movement of antigen-experienced B cells in germinal centers, and CCR6 expression marks memory B-cell precursors in these structures [333–335]. CXCR4 homes long-lived plasma cells to supportive niches in BM and spleen [336,337], and CCR9 and CCR10 direct plasma cell homing to the intestine and mammary gland [338–343].

Concluding remarks

The chemokine network is enormously complex, comprising of a large number of interacting ligands, receptors, and regulatory proteins engaged in overlapping and diverse cellular processes. The induction of migration, particularly of leukocytes, is its central biological purpose, but its influence extends far beyond this. The physiological contribution of the chemokine network is substantial, with fundamental roles in development, homeostasis, immune surveillance, inflammation, protection from infection, tissue repair, and innate and adaptive immunity. Virtually all diseases involve chemokines and their receptors in some way, some more prominently than others, and although clinical translation has been slow, drugs targeting cCKRs have successfully made it to clinic. The first chemokine was discovered over 40 years ago, and our understanding of the chemokines and their receptors is now well

Fig. 4. Expression of chemokine genes in selected mouse tissues under steady-state conditions. By examining graphs generated on The Immunological Genome Project website (www.immgen.org) [351] using their transcriptomic data, the expression of each chemokine, in each of the tissues shown (left hand column), was assigned to one of the seven color-coded 'Expression Level Categories' indicated in the key in the center of the Figure. Expression in the central nervous system (CNS) was estimated by examining ImmGen data on numerous component parts of the CNS. Expression by lymphocytes was included to help indicate whether chemokine expression by secondary lymphoid organs could be attributed to expression by lymphocytes, the dominant cell type in these organs. It was estimated by examining ImmGen data on B cells, CD4+ T cells, and CD8+ T cells. It should be noted that the function of a chemokine in a tissue will depend of where it is expressed: for example, expression by blood vessel endothelial cells may enable leukocyte recruitment from the blood, while their presence elsewhere might help direct leukocytes to specific microanatomical niches, or encourage departure via lymphatic vessels.

advanced. Nonetheless, there is still much to uncover, and chemokines and their receptors are likely to remain prominent in the scientific literature for years to come.

Acknowledgements

Work in RJBN's laboratory is funded by the Medical Research Council (N023625/1; M019764/1) and the Wellcome Trust (206284/Z/17/Z). AM Wilson provided support services, and D Dyer advised on referencing the GAG section. Searching PubMed with 'chemokine' identifies nearly 100 000 articles: the authors apologize to those whose excellent work they have been unable to cite due to space limitations.

Author contributions

Both authors planned the article structure and content. RJBN wrote the text and constructed the Figures. CH reviewed and edited the article, and helped with literature search and referencing.

References

1 Miller MC & Mayo KH (2017) Chemokines from a structural perspective. *Int J Mol Sci* **18**, 2088.
2 Nomiyama H, Osada N & Yoshie O (2013) Systematic classification of vertebrate chemokines based on conserved synteny and evolutionary history. *Genes Cells* **18**, 1–16.
3 Gonzalez E, Kulkarni H, Bolivar H, Mangano A, Sanchez R, Catano G, Nibbs RJ, Freedman BI, Quinones MP, Bamshad MJ *et al*. (2005) The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. *Science* **307**, 1434–1440.
4 Townson JR, Barcellos LF & Nibbs RJB (2002) Gene copy number regulates the production of the human chemokine CCL3-L1. *Eur J Immunol* **32**, 3016–3026.
5 Nakano H & Gunn MD (2001) Gene duplications at the chemokine locus on mouse chromosome 4: multiple strain-specific haplotypes and the deletion of secondary lymphoid-organ chemokine and EBI-1 ligand chemokine genes in the plt mutation. *J Immunol* **166**, 361–369.
6 Guergnon J & Combadière C (2012) Role of chemokines polymorphisms in diseases. *Immunol Lett* **145**, 15–22.
7 Arenzana-Seisdedos F & Parmentier M (2006) Genetics of resistance to HIV infection: role of co-receptors and co-receptor ligands. *Semin Immunol* **18**, 387–403.
8 Murphy PM, Baggiolini M, Charo IF, Hébert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ & Power CA (2000) International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* **52**, 145–176.
9 Zlotnik A & Yoshie O (2000) Chemokines: a new classification system and their role in immunity. *Immunity* **12**, 121–127.
10 Islam SA, Chang DS, Colvin RA, Byrne MH, McCully ML, Moser B, Lira SA, Charo IF & Luster AD (2011) Mouse CCL8, a CCR8 agonist, promotes atopic dermatitis by recruiting IL-5(+) T(H)2 cells. *Nat Immunol* **12**, 167–177.
11 Nibbs RJ, Yang J, Landau NR, Mao JH & Graham GJ (1999) LD78beta, a non-allelic variant of human MIP-1alpha (LD78alpha), has enhanced receptor interactions and potent HIV suppressive activity. *J Biol Chem* **274**, 17478–17483.
12 Bazan JF, Bacon KB, Hardiman G, Wang W, Soo K, Rossi D, Greaves DR, Zlotnik A & Schall TJ (1997) A new class of membrane-bound chemokine with a CX3C motif. *Nature* **385**, 640–644.
13 Matloubian M, David A, Engel S, Ryan JE & Cyster JG (2000) A transmembrane CXC chemokine is a ligand for HIV-coreceptor Bonzo. *Nat Immunol* **1**, 298–304.
14 Garton KJ, Gough PJ, Blobel CP, Murphy G, Greaves DR, Dempsey PJ & Raines EW (2001) Tumor necrosis factor-alpha-converting enzyme (ADAM17) mediates the cleavage and shedding of fractalkine (CX3CL1). *J Biol Chem* **276**, 37993–38001.
15 Tsou CL, Haskell CA & Charo IF (2001) Tumor necrosis factor-alpha-converting enzyme mediates the inducible cleavage of fractalkine. *J Biol Chem* **276**, 44622–44626.
16 Hundhausen C, Misztela D, Berkhout TA, Broadway N, Saftig P, Reiss K, Hartmann D, Fahrenholz F, Postina R, Matthews V *et al*. (2003) The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion. *Blood* **102**, 1186–1195.
17 Gough PJ, Garton KJ, Wille PT, Rychlewski M, Dempsey PJ & Raines EW (2004) A disintegrin and metalloproteinase 10-mediated cleavage and shedding regulates the cell surface expression of CXC chemokine ligand 16. *J Immunol* **172**, 3678–3685.
18 Abel S, Hundhausen C, Mentlein R, Schulte A, Berkhout TA, Broadway N, Hartmann D, Sedlacek R, Dietrich S, Muetze B *et al*. (2004) The transmembrane CXC-chemokine ligand 16 is induced by IFN-gamma and TNF-alpha and shed by the activity of the disintegrin-like metalloproteinase ADAM10. *J Immunol* **172**, 6362–6372.
19 Berahovich RD, Miao Z, Wang Y, Premack B, Howard MC & Schall TJ (2005) Proteolytic activation of alternative CCR1 ligands in inflammation. *J Immunol* **174**, 7341–7351.

20 Miao Z, Premack BA, Wei Z, Wang Y, Gerard C, Showell H, Howard M, Schall TJ & Berahovich R (2007) Proinflammatory proteases liberate a discrete high-affinity functional FPRL1 (CCR12) ligand from CCL23. *J Immunol* **178**, 7395–7404.
21 Yu L, Cecil J, Peng S-B, Schrementi J, Kovacevic S, Paul D, Su EW & Wang J (2006) Identification and expression of novel isoforms of human stromal cell-derived factor 1. *Gene* **374**, 174–179.
22 Janssens R, Struyf S & Proost P (2017) The unique structural and functional features of CXCL12. *Cell Mol Immunol* **14**, 1–13.
23 Connell BJ, Sadir R, Baleux F, Laguri C, Kleman J-P, Luo L, Arenzana-Seisdedos F & Lortat-Jacob H (2016) Heparan sulfate differentially controls CXCL12α- and CXCL12γ-mediated cell migration through differential presentation to their receptor CXCR4. *Sci Signal* **9**, ra107.
24 Monneau Y, Arenzana-Seisdedos F & Lortat-Jacob H (2016) The sweet spot: how GAGs help chemokines guide migrating cells. *J Leukoc Biol* **99**, 935–953.
25 Salanga CL & Handel TM (2011) Chemokine oligomerization and interactions with receptors and glycosaminoglycans: the role of structural dynamics in function. *Exp Cell Res* **317**, 590–601.
26 Sarris M, Masson J-B, Maurin D, Van der Aa LM, Boudinot P, Lortat-Jacob H & Herbomel P (2012) Inflammatory chemokines direct and restrict leukocyte migration within live tissues as glycan-bound gradients. *Curr Biol* **22**, 2375–2382.
27 Weber M, Hauschild R, Schwarz J, Moussion C, de Vries I, Legler DF, Luther SA, Bollenbach T & Sixt M (2013) Interstitial dendritic cell guidance by haptotactic chemokine gradients. *Science* **339**, 328–332.
28 Barinov A, Luo L, Gasse P, Meas-Yedid V, Donnadieu E, Arenzana-Seisdedos F & Vieira P (2017) Essential role of immobilized chemokine CXCL12 in the regulation of the humoral immune response. *Proc Natl Acad Sci USA* **114**, 2319–2324.
29 Nourshargh S & Alon R (2014) Leukocyte migration into inflamed tissues. *Immunity* **41**, 694–707.
30 Handel TM, Johnson Z, Crown SE, Lau EK & Proudfoot AE (2005) Regulation of protein function by glycosaminoglycans–as exemplified by chemokines. *Annu Rev Biochem* **74**, 385–410.
31 Bao X, Moseman EA, Saito H, Petryanik B, Thiriot A, Hatakeyama S, Ito Y, Kawashima H, Yamaguchi Y, Lowe JB *et al*. (2010) Endothelial heparan sulfate controls chemokine presentation in recruitment of lymphocytes and dendritic cells to lymph nodes. *Immunity* **33**, 817–829.
32 Dyer DP, Thomson JM, Hermant A, Jowitt TA, Handel TM, Proudfoot AEI, Day AJ & Milner CM (2014) TSG-6 inhibits neutrophil migration via direct interaction with the chemokine CXCL8. *J Immunol* **192**, 2177–2185.
33 Dyer DP, Salanga CL, Johns SC, Valdambrini E, Fuster MM, Milner CM, Day AJ & Handel TM (2016) The anti-inflammatory protein TSG-6 regulates chemokine function by inhibiting chemokine/glycosaminoglycan interactions. *J Biol Chem* **291**, 12627–12640.
34 Adage T, Piccinini A-M, Falsone A, Trinker M, Robinson J, Gesslbauer B & Kungl AJ (2012) Structure-based design of decoy chemokines as a way to explore the pharmacological potential of glycosaminoglycans. *Br J Pharmacol* **167**, 1195–1205.
35 Lohmann N, Schirmer L, Atallah P, Wandel E, Ferrer RA, Werner C, Simon JC, Franz S & Freudenberg U (2017) Glycosaminoglycan-based hydrogels capture inflammatory chemokines and rescue defective wound healing in mice. *Sci Transl Med* **9**, eaai9044.
36 Dyer DP, Salanga CL, Volkman BF, Kawamura T & Handel TM (2016) The dependence of chemokine-glycosaminoglycan interactions on chemokine oligomerization. *Glycobiology* **26**, 312–326.
37 Liang WG, Triandafillou CG, Huang T-Y, Zulueta MML, Banerjee S, Dinner AR, Hung S-C & Tang W-J (2016) Structural basis for oligomerization and glycosaminoglycan binding of CCL5 and CCL3. *Proc Natl Acad Sci USA* **113**, 5000–5005.
38 von Hundelshausen P, Koenen RR, Sack M, Mause SF, Adriaens W, Proudfoot AEI, Hackeng TM & Weber C (2005) Heterophilic interactions of platelet factor 4 and RANTES promote monocyte arrest on endothelium. *Blood* **105**, 924–930.
39 Koenen RR, von Hundelshausen P, Nesmelova IV, Zernecke A, Liehn EA, Sarabi A, Kramp BK, Piccinini AM, Paludan SR, Kowalska MA *et al*. (2009) Disrupting functional interactions between platelet chemokines inhibits atherosclerosis in hyperlipidemic mice. *Nat Med* **15**, 97–103.
40 vonHundelshausen P, Agten SM, Eckardt V, Blanchet X, Schmitt MM, Ippel H, Neideck C, Bidzhekov K, Leberzammer J, Wichapong K *et al*. (2017) Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation. *Sci Transl Med* **9**, eaah6650.
41 Proudfoot AEI, Handel TM, Johnson Z, Lau EK, LiWang P, Clark-Lewis I, Borlat F, Wells TNC & Kosco-Vilbois MH (2003) Glycosaminoglycan binding and oligomerization are essential for the in vivo activity of certain chemokines. *Proc Natl Acad Sci USA* **100**, 1885–1890.
42 Loos T, Mortier A, Gouwy M, Ronsse I, Put W, Lenaerts J-P, Van Damme J & Proost P (2008) Citrullination of CXCL10 and CXCL11 by peptidylarginine deiminase: a naturally occurring

posttranslational modification of chemokines and new dimension of immunoregulation. *Blood* **112**, 2648–2656.
43 Struyf S, Noppen S, Loos T, Mortier A, Gouwy M, Verbeke H, Huskens D, Luangsay S, Parmentier M, Geboes K *et al.* (2009) Citrullination of CXCL12 differentially reduces CXCR4 and CXCR7 binding with loss of inflammatory and anti-HIV-1 activity via CXCR4. *J Immunol* **182**, 666–674.
44 Proost P, Loos T, Mortier A, Schutyser E, Gouwy M, Noppen S, Dillen C, Ronsse I, Conings R, Struyf S *et al.* (2008) Citrullination of CXCL8 by peptidylarginine deiminase alters receptor usage, prevents proteolysis, and dampens tissue inflammation. *J Exp Med* **205**, 2085–2097.
45 Barker CE, Thompson S, O'Boyle G, Lortat-Jacob H, Sheerin NS, Ali S & Kirby JA (2017) CCL2 nitration is a negative regulator of chemokine-mediated inflammation. *Sci Rep* **7**, 44384.
46 Molon B, Ugel S, Del Pozzo F, Soldani C, Zilio S, Avella D, De Palma A, Mauri P, Monegal A, Rescigno M *et al.* (2011) Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. *J Exp Med* **208**, 1949–1962.
47 Janssens R, Mortier A, Boff D, Vanheule V, Gouwy M, Franck C, Larsen O, Rosenkilde MM, Van Damme J, Amaral FA *et al.* (2016) Natural nitration of CXCL12 reduces its signaling capacity and chemotactic activity in vitro and abrogates intra-articular lymphocyte recruitment in vivo. *Oncotarget* **7**, 62439–62459.
48 Metzemaekers M, Van Damme J, Mortier A & Proost P (2016) Regulation of chemokine activity – a focus on the role of dipeptidyl peptidase IV/CD26. *Front Immunol* **7**, 483.
49 Proost P, Struyf S, Van Damme J, Fiten P, Ugarte-Berzal E & Opdenakker G (2017) Chemokine isoforms and processing in inflammation and immunity. *J Autoimmun* **85**, 45–57.
50 Van Lint P & Libert C (2007) Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation. *J Leukoc Biol* **82**, 1375–1381.
51 Schumann K, Lämmermann T, Bruckner M, Legler DF, Polleux J, Spatz JP, Schuler G, Förster R, Lutz MB & Sorokin L (2010) Immobilized chemokine fields and soluble chemokine gradients cooperatively shape migration patterns of dendritic cells. *Immunity* **32**, 703–713.
52 Starr AE, Dufour A, Maier J & Overall CM (2011) Biochemical analysis of matrix metalloproteinase activation of chemokines CCL15 and CCL23 and increased glycosaminoglycan binding of CCL16. *J Biol Chem* **287**, 5848–5860.
53 Li Q, Park PW, Wilson CL & Parks WC (2002) Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. *Cell* **111**, 635–646.
54 Barreira da Silva R, Laird ME, Yatim N, Fiette L, Ingersoll MA & Albert ML (2015) Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and immunotherapy. *Nat Immunol* **16**, 850–858.
55 Farzan M, Mirzabekov T, Kolchinsky P, Wyatt R, Cayabyab M, Gerard NP, Gerard C, Sodroski J & Choe H (1999) Tyrosine sulfation of the amino terminus of CCR5 facilitates HIV-1 entry. *Cell* **96**, 667–676.
56 Tan JHY, Ludeman JP, Wedderburn J, Canals M, Hall P, Butler SJ, Taleski D, Christopoulos A, Hickey MJ, Payne RJ *et al.* (2013) Tyrosine sulfation of chemokine receptor CCR2 enhances interactions with both monomeric and dimeric forms of the chemokine monocyte chemoattractant protein-1 (MCP-1). *J Biol Chem* **288**, 10024–10034.
57 Millard CJ, Ludeman JP, Canals M, Bridgford JL, Hinds MG, Clayton DJ, Christopoulos A, Payne RJ & Stone MJ (2014) Structural basis of receptor sulfotyrosine recognition by a CC chemokine: the N-terminal region of CCR3 bound to CCL11/eotaxin-1. *Structure* **22**, 1571–1581.
58 Bannert N, Craig S, Farzan M, Sogah D, Santo NV, Choe H & Sodroski J (2001) Sialylated O-glycans and sulfated tyrosines in the NH2-terminal domain of CC chemokine receptor 5 contribute to high affinity binding of chemokines. *J Exp Med* **194**, 1661–1673.
59 Gutiérrez J, Kremer L, Zaballos A, Goya I, Martínez-A C & Márquez G (2004) Analysis of post-translational CCR8 modifications and their influence on receptor activity. *J Biol Chem* **279**, 14726–14733.
60 Colvin RA, Campanella GSV, Manice LA & Luster AD (2006) CXCR3 requires tyrosine sulfation for ligand binding and a second extracellular loop arginine residue for ligand-induced chemotaxis. *Mol Cell Biol* **26**, 5838–5849.
61 Farzan M, Babcock GJ, Vasilieva N, Wright PL, Kiprilov E, Mirzabekov T & Choe H (2002) The role of post-translational modifications of the CXCR4 amino terminus in stromal-derived factor 1 alpha association and HIV-1 entry. *J Biol Chem* **277**, 29484–29489.
62 Fong AM, Alam SM, Imai T, Haribabu B & Patel DD (2002) CX3CR1 tyrosine sulfation enhances fractalkine-induced cell adhesion. *J Biol Chem* **277**, 19418–19423.
63 Kiermaier E, Moussion C, Veldkamp CT, Gerardy-Schahn R, de Vries I, Williams LG, Chaffee GR, Phillips AJ, Freiberger F, Imre R *et al.* (2016) Polysialylation controls dendritic cell trafficking by regulating chemokine recognition. *Science* **351**, 186–190.
64 Kleist AB, Getschman AE, Ziarek JJ, Nevins AM, Gauthier P-A, Chevigné A, Szpakowska M &

Volkman BF (2016) New paradigms in chemokine receptor signal transduction: moving beyond the two-site model. *Biochem Pharmacol* **114**, 53–68.
65 Kufareva I, Salanga CL & Handel TM (2015) Chemokine and chemokine receptor structure and interactions: implications for therapeutic strategies. *Immunol Cell Biol* **93**, 372–383.
66 Bachelerie F, Ben-Baruch A, Burkhardt AM, Combadière C, Farber JM, Graham GJ, Horuk R, Sparre-Ulrich AH, Locati M, Luster AD *et al*. (2014) International Union of Pharmacology. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. *Pharmacol Rev* **66**, 1–79.
67 Kehrl JH (2006) Chemoattractant receptor signaling and the control of lymphocyte migration. *Immunol Res* **34**, 211–227.
68 Maravillas-Montero JL, Burkhardt AM, Hevezi PA, Carnevale CD, Smit MJ & Zlotnik A (2015) Cutting edge: GPR35/CXCR8 is the receptor of the mucosal chemokine CXCL17. *J Immunol* **194**, 29–33.
69 Charo IF, Myers SJ, Herman A, Franci C, Connolly AJ & Coughlin SR (1994) Molecular cloning and functional expression of two monocyte chemoattractant protein 1 receptors reveals alternative splicing of the carboxyl-terminal tails. *Proc Natl Acad Sci USA* **91**, 2752–2756.
70 Wong LM, Myers SJ, Tsou CL, Gosling J, Arai H & Charo IF (1997) Organization and differential expression of the human monocyte chemoattractant protein 1 receptor gene. Evidence for the role of the carboxyl-terminal tail in receptor trafficking. *J Biol Chem* **272**, 1038–1045.
71 Yu CR, Peden KW, Zaitseva MB, Golding H & Farber JM (2000) CCR9A and CCR9B: two receptors for the chemokine CCL25/TECK/Ck beta-15 that differ in their sensitivities to ligand. *J Immunol* **164**, 1293–1305.
72 Gupta SK & Pillarisetti K (1999) Cutting edge: CXCR4-Lo: molecular cloning and functional expression of a novel human CXCR4 splice variant. *J Immunol* **163**, 2368–2372.
73 Lasagni L, Francalanci M, Annunziato F, Lazzeri E, Giannini S, Cosmi L, Sagrinati C, Mazzinghi B, Orlando C, Maggi E *et al*. (2003) An alternatively spliced variant of CXCR3 mediates the inhibition of endothelial cell growth induced by IP-10, Mig, and I-TAC, and acts as functional receptor for platelet factor 4. *J Exp Med* **197**, 1537–1549.
74 Ehlert JE, Addison CA, Burdick MD, Kunkel SL & Strieter RM (2004) Identification and partial characterization of a variant of human CXCR3 generated by posttranscriptional exon skipping. *J Immunol* **173**, 6234–6240.
75 Wu B, Chien EYT, Mol CD, Fenalti G, Liu W, Katritch V, Abagyan R, Brooun A, Wells P, Bi FC *et al*. (2010) Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science* **330**, 1066–1071.
76 Tan Q, Zhu Y, Li J, Chen Z, Han GW, Kufareva I, Li T, Ma L, Fenalti G, Li J *et al*. (2013) Structure of the CCR5 chemokine receptor-HIV entry inhibitor maraviroc complex. *Science* **341**, 1387–1390.
77 Qin L, Kufareva I, Holden LG, Wang C, Zheng Y, Zhao C, Fenalti G, Wu H, Han GW, Cherezov V *et al*. (2015) Structural biology. Crystal structure of the chemokine receptor CXCR4 in complex with a viral chemokine. *Science* **347**, 1117–1122.
78 Burg JS, Ingram JR, Venkatakrishnan AJ, Jude KM, Dukkipati A, Feinberg EN, Angelini A, Waghray D, Dror RO, Ploegh HL *et al*. (2015) Structural biology. Structural basis for chemokine recognition and activation of a viral G protein-coupled receptor. *Science* **347**, 1113–1117.
79 Zheng Y, Qin L, Zacarías NVO, deVries H, Han GW, Gustavsson M, Dabros M, Zhao C, Cherney RJ, Carter P *et al*. (2016) Structure of CC chemokine receptor 2 with orthosteric and allosteric antagonists. *Nature* **540**, 458–461.
80 Zheng Y, Han GW, Abagyan R, Wu B, Stevens RC, Cherezov V, Kufareva I & Handel TM (2017) Structure of CC chemokine receptor 5 with a potent chemokine antagonist reveals mechanisms of chemokine recognition and molecular mimicry by HIV. *Immunity* **46** (1005–1017), e5.
81 Oswald C, Rappas M, Kean J, Doré AS, Errey JC, Bennett K, Deflorian F, Christopher JA, Jazayeri A, Mason JS *et al*. (2016) Intracellular allosteric antagonism of the CCR9 receptor. *Nature* **540**, 462–465.
82 Ziarek JJ, Kleist AB, London N, Raveh B, Montpas N, Bonneterre J, St-Onge G, DiCosmo-Ponticello CJ, Koplinski CA, Roy I *et al*. (2017) Structural basis for chemokine recognition by a G protein-coupled receptor and implications for receptor activation. *Sci Signal* **10**, eaah5756.
83 Gustavsson M, Wang L, van Gils N, Stephens BS, Zhang P, Schall TJ, Yang S, Abagyan R, Chance MR, Kufareva I *et al*. (2017) Structural basis of ligand interaction with atypical chemokine receptor 3. *Nat Commun* **8**, 14135.
84 Kufareva I, Gustavsson M, Zheng Y, Stephens BS & Handel TM (2017) What do structures tell us about chemokine receptor function and antagonism? *Annu Rev Biophys* **46**, 175–198.
85 Corbisier J, Galès C, Huszagh A, Parmentier M & Springael J-Y (2015) Biased signaling at chemokine receptors. *J Biol Chem* **290**, 9542–9554.
86 Steen A, Larsen O, Thiele S & Rosenkilde MM (2014) Biased and g protein-independent signaling of chemokine receptors. *Front Immunol* **5**, 277.

87 Hauser MA, Schaeuble K, Kindinger I, Impellizzieri D, Krueger WA, Hauck CR, Boyman O & Legler DF (2016) Inflammation-induced CCR7 oligomers form scaffolds to integrate distinct signaling pathways for efficient cell migration. *Immunity* **44**, 59–72.
88 Zweemer AJM, Toraskar J, Heitman LH & IJzerman AP (2014) Bias in chemokine receptor signalling. *Trends Immunol* **35**, 243–252.
89 Yang D, Chertov O, Bykovskaia SN, Chen Q, Buffo MJ, Shogan J, Anderson M, Schröder JM, Wang JM, Howard OM *et al*. (1999) Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* **286**, 525–528.
90 Tirone M, Tran NL, Ceriotti C, Gorzanelli A, Canepari M, Bottinelli R, Raucci A, Di Maggio S, Santiago C, Mellado M *et al*. (2018) High mobility group box 1 orchestrates tissue regeneration via CXCR4. *J Exp Med* **215**, 303–318.
91 Schiraldi M, Raucci A, Muñoz LM, Livoti E, Celona B, Vénéreau E, Apuzzo T, De Marchis F, Pedotti M, Bachi A *et al*. (2012) HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4. *J Exp Med* **209**, 551–563.
92 Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, Dewor M, Georgiev I, Schober A, Leng L *et al*. (2007) MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. *Nat Med* **13**, 587–596.
93 Chakera A, Seeber RM, John AE, Eidne KA & Greaves DR (2008) The duffy antigen/receptor for chemokines exists in an oligomeric form in living cells and functionally antagonizes CCR5 signaling through hetero-oligomerization. *Mol Pharmacol* **73**, 1362–1370.
94 Agrawal L, Lu X, Qingwen J, VanHorn-Ali Z, Nicolescu IV, McDermott DH, Murphy PM & Alkhatib G (2004) Role for CCR5Delta32 protein in resistance to R5, R5X4, and X4 human immunodeficiency virus type 1 in primary CD4+ cells. *J Virol* **78**, 2277–2287.
95 Mellado M, Rodriguez-Frade JM, Vila-Coro AJ, Fernández S, Martín de Ana A, Jones DR, Torán JL & Martinez-A C (2001) Chemokine receptor homo- or heterodimerization activates distinct signaling pathways. *EMBO J* **20**, 2497–2507.
96 Percherancier Y, Berchiche YA, Slight I, Volkmer-Engert R, Tamamura H, Fujii N, Bouvier M & Heveker N (2005) Bioluminescence resonance energy transfer reveals ligand-induced conformational changes in CXCR4 homo- and heterodimers. *J Biol Chem* **280**, 9895–9903.
97 Sohy D, Yano H, de Nadai P, Urizar E, Guillabert A, Javitch JA, Parmentier M & Springael J-Y (2009) Hetero-oligomerization of CCR2, CCR5, and CXCR4 and the protean effects of "selective" antagonists. *J Biol Chem* **284**, 31270–31279.
98 Wilson S, Wilkinson G & Milligan G (2005) The CXCR1 and CXCR2 receptors form constitutive homo- and heterodimers selectively and with equal apparent affinities. *J Biol Chem* **280**, 28663–28674.
99 Sierro F, Biben C, Martínez-Muñoz L, Mellado M, Ransohoff RM, Li M, Woehl B, Leung H, Groom J, Batten M *et al*. (2007) Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7. *Proc Natl Acad Sci USA* **104**, 14759–14764.
100 Levoye A, Balabanian K, Baleux F, Bachelerie F & Lagane B (2009) CXCR7 heterodimerizes with CXCR4 and regulates CXCL12-mediated G protein signaling. *Blood* **113**, 6085–6093.
101 Watts AO, van Lipzig MMH, Jaeger WC, Seeber RM, van Zwam M, Vinet J, van der Lee MMC, Siderius M, Zaman GJR, Boddeke HWGM *et al*. (2013) Identification and profiling of CXCR3-CXCR4 chemokine receptor heteromer complexes. *Br J Pharmacol* **168**, 1662–1674.
102 Schwartz V, Lue H, Kraemer S, Korbiel J, Krohn R, Ohl K, Bucala R, Weber C & Bernhagen J (2009) A functional heteromeric MIF receptor formed by CD74 and CXCR4. *FEBS Lett* **583**, 2749–2757.
103 Chen C, Li J, Bot G, Szabo I, Rogers TJ & Liu-Chen L-Y (2004) Heterodimerization and cross-desensitization between the mu-opioid receptor and the chemokine CCR5 receptor. *Eur J Pharmacol* **483**, 175–186.
104 Parenty G, Appelbe S & Milligan G (2008) CXCR2 chemokine receptor antagonism enhances DOP opioid receptor function via allosteric regulation of the CXCR2-DOP receptor heterodimer. *Biochem J* **412**, 245–256.
105 Coke CJ, Scarlett KA, Chetram MA, Jones KJ, Sandifer BJ, Davis AS, Marcus AI & Hinton CV (2016) Simultaneous activation of induced heterodimerization between CXCR4 chemokine receptor and cannabinoid receptor 2 (CB2) reveals a mechanism for regulation of tumor progression. *J Biol Chem* **291**, 9991–10005.
106 Pello OM, Martínez-Muñoz L, Parrillas V, Serrano A, Rodríguez-Frade JM, Toro MJ, Lucas P, Monterrubio M, Martínez-A C & Mellado M (2008) Ligand stabilization of CXCR4/delta-opioid receptor heterodimers reveals a mechanism for immune response regulation. *Eur J Immunol* **38**, 537–549.
107 Kumar A, Humphreys TD, Kremer KN, Bramati PS, Bradfield L, Edgar CE & Hedin KE (2006) CXCR4 physically associates with the T cell receptor to signal in T cells. *Immunity* **25**, 213–224.

108 Kremer KN, Clift IC, Miamen AG, Bamidele AO, Qian N-X, Humphreys TD & Hedin KE (2011) Stromal cell-derived factor-1 signaling via the CXCR4-TCR heterodimer requires phospholipase C-β3 and phospholipase C-γ1 for distinct cellular responses. *J Immunol* **187**, 1440–1447.

109 Suzuki S, Chuang LF, Yau P, Doi RH & Chuang RY (2002) Interactions of opioid and chemokine receptors: oligomerization of mu, kappa, and delta with CCR5 on immune cells. *Exp Cell Res* **280**, 192–200.

110 Herrera C, Morimoto C, Blanco J, Mallol J, Arenzana F, Lluis C & Franco R (2001) Comodulation of CXCR4 and CD26 in human lymphocytes. *J Biol Chem* **276**, 19532–19539.

111 Xiao X, Wu L, Stantchev TS, Feng YR, Ugolini S, Chen H, Shen Z, Riley JL, Broder CC, Sattentau QJ *et al.* (1999) Constitutive cell surface association between CD4 and CCR5. *Proc Natl Acad Sci USA* **96**, 7496–7501.

112 Tripathi A, Vana PG, Chavan TS, Brueggemann LI, Byron KL, Tarasova NI, Volkman BF, Gaponenko V & Majetschak M (2015) Heteromerization of chemokine (C-X-C motif) receptor 4 with α1A/B-adrenergic receptors controls α1-adrenergic receptor function. *Proc Natl Acad Sci USA* **112**, E1659–E1668.

113 Barroso R, Martínez-Muñoz L, Barrondo S, Vega B, Holgado BL, Lucas P, Baíllo A, Sallés J, Rodríguez-Frade JM & Mellado M (2012) EBI2 regulates CXCL13-mediated responses by heterodimerization with CXCR5. *FASEB J* **26**, 4841–4854.

114 Martínez-Muñoz L, Barroso R, Dyrhaug SY, Navarro G, Lucas P, Soriano SF, Vega B, Costas C, Muñoz-Fernández MÁ, Santiago C *et al.* (2014) CCR5/CD4/CXCR4 oligomerization prevents HIV-1 gp120IIIB binding to the cell surface. *Proc Natl Acad Sci USA* **111**, E1960–E1969.

115 Moreno-Fernandez ME, Aliberti J, Groeneweg S, Köhl J & Chougnet CA (2016) A novel role for the receptor of the complement cleavage fragment C5a, C5aR1, in CCR5-mediated entry of HIV into macrophages. *AIDS Res Hum Retroviruses* **32**, 399–408.

116 LaRocca TJ, Schwarzkopf M, Altman P, Zhang S, Gupta A, Gomes I, Alvin Z, Champion HC, Haddad G, Hajjar RJ *et al.* (2010) β2-Adrenergic receptor signaling in the cardiac myocyte is modulated by interactions with CXCR4. *J Cardiovasc Pharmacol* **56**, 548–559.

117 Catalano M, Trettel F, Cipriani R, Lauro C, Sobrero F, Eusebi F & Limatola C (2008) Chemokine CXCL8 modulates GluR1 phosphorylation. *J Neuroimmunol* **198**, 75–81.

118 Hayasaka H, Kobayashi D, Yoshimura H, Nakayama EE, Shioda T & Miyasaka M (2015) The HIV-1 Gp120/CXCR4 axis promotes CCR7 ligand-dependent CD4 T cell migration: CCR7 homo- and CCR7/CXCR4 hetero-oligomer formation as a possible mechanism for up-regulation of functional CCR7. *PLoS ONE* **10**, e0117454.

119 Nibbs RJ, Salcedo TW, Campbell JD, Yao XT, Li Y, Nardelli B, Olsen HS, Morris TS, Proudfoot AE, Patel VP *et al.* (2000) C-C chemokine receptor 3 antagonism by the beta-chemokine macrophage inflammatory protein 4, a property strongly enhanced by an amino-terminal alanine-methionine swap. *J Immunol* **164**, 1488–1497.

120 Loetscher P, Pellegrino A, Gong JH, Mattioli I, Loetscher M, Bardi G, Baggiolini M & Clark-Lewis I (2001) The ligands of CXC chemokine receptor 3, I-TAC, Mig, and IP10, are natural antagonists for CCR3. *J Biol Chem* **276**, 2986–2991.

121 Petkovic V, Moghini C, Paoletti S, Uguccioni M & Gerber B (2004) Eotaxin-3/CCL26 is a natural antagonist for CC chemokine receptors 1 and 5. A human chemokine with a regulatory role. *J Biol Chem* **279**, 23357–23363.

122 Petkovic V, Moghini C, Paoletti S, Uguccioni M & Gerber B (2004) I-TAC/CXCL11 is a natural antagonist for CCR5. *J Leukoc Biol* **76**, 701–708.

123 Weng Y, Siciliano SJ, Waldburger KE, Sirotina-Meisher A, Staruch MJ, Daugherty BL, Gould SL, Springer MS & DeMartino JA (1998) Binding and functional properties of recombinant and endogenous CXCR3 chemokine receptors. *J Biol Chem* **273**, 18288–18291.

124 Ogilvie P, Paoletti S, Clark-Lewis I & Uguccioni M (2003) Eotaxin-3 is a natural antagonist for CCR2 and exerts a repulsive effect on human monocytes. *Blood* **102**, 789–794.

125 Ogilvie P, Bardi G, Clark-Lewis I, Baggiolini M & Uguccioni M (2001) Eotaxin is a natural antagonist for CCR2 and an agonist for CCR5. *Blood* **97**, 1920–1924.

126 Xanthou G, Duchesnes CE, Williams TJ & Pease JE (2003) CCR3 functional responses are regulated by both CXCR3 and its ligands CXCL9, CXCL10 and CXCL11. *Eur J Immunol* **33**, 2241–2250.

127 Chen J, Yao Y, Gong C, Yu F, Su S, Chen J, Liu B, Deng H, Wang F, Lin L *et al.* (2011) CCL18 from tumor-associated macrophages promotes breast cancer metastasis via PITPNM3. *Cancer Cell* **19**, 541–555.

128 Islam SA, Ling MF, Leung J, Shreffler WG & Luster AD (2013) Identification of human CCR8 as a CCL18 receptor. *J Exp Med* **210**, 1889–1898.

129 Alcami A & Lira SA (2010) Modulation of chemokine activity by viruses. *Curr Opin Immunol* **22**, 482–487.

130 Déruaz M, Frauenschuh A, Alessandri AL, Dias JM, Coelho FM, Russo RC, Ferreira BR, Graham GJ, Shaw JP, Wells TNC *et al.* (2008) Ticks produce highly selective chemokine binding proteins with antiinflammatory activity. *J Exp Med* **205**, 2019–2031.

131 Bonvin P, Power CA & Proudfoot AEI (2016) Evasins: therapeutic potential of a new family of chemokine-binding proteins from ticks. *Front Immunol* **7**, 208.
132 Hayward J, Sanchez J, Perry A, Huang C, Rodriguez Valle M, Canals M, Payne RJ & Stone MJ (2017) Ticks from diverse genera encode chemokine-inhibitory evasin proteins. *J Biol Chem* **292**, 15670–15680.
133 Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhart M, Di Marzio P, Marmon S, Sutton RE, Hill CM *et al.* (1996) Identification of a major co-receptor for primary isolates of HIV-1. *Nature* **381**, 661–666.
134 Feng Y, Broder CC, Kennedy PE & Berger EA (1996) HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* **272**, 872–877.
135 Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP *et al.* (1996) HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* **381**, 667–673.
136 Alkhatib G, Combadière C, Broder CC, Feng Y, Kennedy PE, Murphy PM & Berger EA (1996) CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* **272**, 1955–1958.
137 Cocchi F, DeVico AL, Garzino-Demo A, Cara A, Gallo RC & Lusso P (1996) The V3 domain of the HIV-1 gp120 envelope glycoprotein is critical for chemokine-mediated blockade of infection. *Nat Med* **2**, 1244–1247.
138 Speck RF, Wehrly K, Platt EJ, Atchison RE, Charo IF, Kabat D, Chesebro B & Goldsmith MA (1997) Selective employment of chemokine receptors as human immunodeficiency virus type 1 coreceptors determined by individual amino acids within the envelope V3 loop. *J Virol* **71**, 7136–7139.
139 Wu L, Gerard NP, Wyatt R, Choe H, Parolin C, Ruffing N, Borsetti A, Cardoso AA, Desjardin E, Newman W *et al.* (1996) CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5. *Nature* **384**, 179–183.
140 Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, MacDonald ME, Stuhlmann H, Koup RA & Landau NR (1996) Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* **86**, 367–377.
141 Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C *et al.* (1996) Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* **382**, 722–725.
142 Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E *et al.* (1996) Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* **273**, 1856–1862.
143 Woollard SM & Kanmogne GD (2015) Maraviroc: a review of its use in HIV infection and beyond. *Drug Des Devel Ther* **9**, 5447–5468.
144 Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, Schneider T, Hofmann J, Kücherer C, Blau O *et al.* (2009) Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* **360**, 692–698.
145 Glass WG, McDermott DH, Lim JK, Lekhong S, Yu SF, Frank WA, Pape J, Cheshier RC & Murphy PM (2006) CCR5 deficiency increases risk of symptomatic West Nile virus infection. *J Exp Med* **203**, 35–40.
146 Glass WG, Lim JK, Cholera R, Pletnev AG, Gao J-L & Murphy PM (2005) Chemokine receptor CCR5 promotes leukocyte trafficking to the brain and survival in West Nile virus infection. *J Exp Med* **202**, 1087–1098.
147 Aliberti J, Valenzuela JG, Carruthers VB, Hieny S, Andersen J, Charest H, Reis e Sousa C, Fairlamb A, Ribeiro JM & Sher A (2003) Molecular mimicry of a CCR5 binding-domain in the microbial activation of dendritic cells. *Nat Immunol* **4**, 485–490.
148 Zhivaki D, Lemoine S, Lim A, Morva A, Vidalain P-O, Schandene L, Casartelli N, Rameix-Welti M-A, Hervé P-L, Deriaud E *et al.* (2017) Respiratory syncytial virus infects regulatory B cells in human neonates via chemokine receptor CX3CR1 and promotes lung disease severity. *Immunity* **46**, 301–314.
149 Spaan AN, Vrieling M, Wallet P, Badiou C, Reyes-Robles T, Ohneck EA, Benito Y, de Haas CJC, Day CJ, Jennings MP *et al.* (2014) The staphylococcal toxins γ-haemolysin AB and CB differentially target phagocytes by employing specific chemokine receptors. *Nat Commun* **5**, 5438.
150 Spaan AN, Reyes-Robles T, Badiou C, Cochet S, Boguslawski KM, Yoong P, Day CJ, de Haas CJC, van Kessel KPM, Vandenesch F *et al.* (2015) *Staphylococcus aureus* targets the Duffy antigen receptor for chemokines (DARC) to lyse erythrocytes. *Cell Host Microbe* **18**, 363–370.
151 Alonzo F, Kozhaya L, Rawlings SA, Reyes-Robles T, DuMont AL, Myszka DG, Landau NR, Unutmaz D & Torres VJ (2013) CCR5 is a receptor for *Staphylococcus aureus* leukotoxin ED. *Nature* **493**, 51–55.
152 Reyes-Robles T, Alonzo F, Kozhaya L, Lacy DB, Unutmaz D & Torres VJ (2013) *Staphylococcus aureus* Leukotoxin ED targets the chemokine receptors

CXCR1 and CXCR2 to kill leukocytes and promote infection. *Cell Host Microbe* **14**, 453–459.
153 Nibbs RJB & Graham GJ. Immune regulation by atypical chemokine receptors. *Nat Rev Immunol* **13**, 815–829.
154 Nibbs RJB & Graham GJ (2013) Immune regulation by atypical chemokine receptors. *Nat Rev Immunol* **13**, 815–829.
155 Choe H, Moore MJ, Owens CM, Wright PL, Vasilieva N, Li W, Singh AP, Shakri R, Chitnis CE & Farzan M (2005) Sulphated tyrosines mediate association of chemokines and *Plasmodium vivax* Duffy binding protein with the Duffy antigen/receptor for chemokines (DARC). *Mol Microbiol* **55**, 1413–1422.
156 Hewit KD, Fraser A, Nibbs RJB & Graham GJ (2014) The N-terminal region of the atypical chemokine receptor ACKR2 is a key determinant of ligand binding. *J Biol Chem* **289**, 12330–12342.
157 Pruenster M, Mudde L, Bombosi P, Dimitrova S, Zsak M, Middleton J, Richmond A, Graham GJ, Segerer S, Nibbs RJB *et al*. (2009) The Duffy antigen receptor for chemokines transports chemokines and supports their promigratory activity. *Nat Immunol* **10**, 101–108.
158 Lee JS, Frevert CW, Wurfel MM, Peiper SC, Wong VA, Ballman KK, Ruzinski JT, Rhim JS, Martin TR & Goodman RB (2003) Duffy antigen facilitates movement of chemokine across the endothelium in vitro and promotes neutrophil transmigration in vitro and in vivo. *J Immunol* **170**, 5244–5251.
159 Fukuma N, Akimitsu N, Hamamoto H, Kusuhara H, Sugiyama Y & Sekimizu K (2003) A role of the Duffy antigen for the maintenance of plasma chemokine concentrations. *Biochem Biophys Res Commun* **303**, 137–139.
160 Mayr FB, Spiel AO, Leitner JM, Firbas C, Schnee J, Hilbert J, Derendorf H & Jilma B (2009) Influence of the Duffy antigen on pharmacokinetics and pharmacodynamics of recombinant monocyte chemoattractant protein (MCP-1, CCL-2) in vivo. *Int J Immunopathol Pharmacol* **22**, 615–625.
161 Jilma-Stohlawetz P, Homoncik M, Drucker C, Marsik C, Rot A, Mayr WR, Seibold B & Jilma B (2001) Fy phenotype and gender determine plasma levels of monocyte chemotactic protein. *Transfusion* **41**, 378–381.
162 Schnabel RB, Baumert J, Barbalic M, Dupuis J, Ellinor PT, Durda P, Dehghan A, Bis JC, Illig T, Morrison AC *et al*. (2010) Duffy antigen receptor for chemokines (Darc) polymorphism regulates circulating concentrations of monocyte chemoattractant protein-1 and other inflammatory mediators. *Blood* **115**, 5289–5299.
163 Mei J, Liu Y, Dai N, Favara M, Greene T, Jeyaseelan S, Poncz M, Lee JS & Worthen GS (2010) CXCL5 regulates chemokine scavenging and pulmonary host defense to bacterial infection. *Immunity* **33**, 106–117.
164 Duchene J, Novitzky-Basso I, Thiriot A, Casanova-Acebes M, Bianchini M, Etheridge SL, Hub E, Nitz K, Artinger K, Eller K *et al*. (2017) Atypical chemokine receptor 1 on nucleated erythroid cells regulates hematopoiesis. *Nat Immunol* **18**, 753–761.
165 Reich D, Nalls MA, Kao WHL, Akylbekova EL, Tandon A, Patterson N, Mullikin J, Hsueh W-C, Cheng C-Y, Coresh J *et al*. (2009) Reduced neutrophil count in people of African descent is due to a regulatory variant in the Duffy antigen receptor for chemokines gene. *PLoS Genet* **5**, e1000360.
166 Horuk R, Chitnis CE, Darbonne WC, Colby TJ, Rybicki A, Hadley TJ & Miller LH (1993) A receptor for the malarial parasite *Plasmodium vivax*: the erythrocyte chemokine receptor. *Science* **261**, 1182–1184.
167 Batchelor JD, Malpede BM, Omattage NS, DeKoster GT, Henzler-Wildman KA & Tolia NH (2014) Red blood cell invasion by *Plasmodium vivax*: structural basis for DBP engagement of DARC. *PLoS Pathog* **10**, e1003869.
168 Wertheimer SP & Barnwell JW (1989) Plasmodium vivax interaction with the human Duffy blood group glycoprotein: identification of a parasite receptor-like protein. *Exp Parasitol* **69**, 340–350.
169 Zimmerman PA, Ferreira MU, Howes RE & Mercereau-Puijalon O (2013) Red blood cell polymorphism and susceptibility to *Plasmodium vivax*. *Adv Parasitol* **81**, 27–76.
170 Tournamille C, Colin Y, Cartron JP & Le Van Kim C (1995) Disruption of a GATA motif in the Duffy gene promoter abolishes erythroid gene expression in Duffy-negative individuals. *Nat Genet* **10**, 224–228.
171 Crosslin DR, McDavid A, Weston N, Nelson SC, Zheng X, Hart E, de Andrade M, Kullo IJ, McCarty CA, Doheny KF *et al*. & Network TEMRAGE (2012) Genetic variants associated with the white blood cell count in 13,923 subjects in the eMERGE Network. *Hum Genet* **131**, 639–652.
172 Nalls MA, Wilson JG, Patterson NJ, Tandon A, Zmuda JM, Huntsman S, Garcia M, Hu D, Li R, Beamer BA *et al*. (2008) Admixture mapping of white cell count: genetic locus responsible for lower white blood cell count in the Health ABC and Jackson Heart studies. *Am J Hum Genet* **82**, 81–87.
173 Kulkarni H, Marconi VC, He W, Landrum ML, Okulicz JF, Delmar J, Kazandjian D, Castiblanco J, Ahuja SS, Wright EJ *et al*. (2009) The Duffy-null state is associated with a survival advantage in leukopenic HIV-infected persons of African ancestry. *Blood* **114**, 2783–2792.
174 He W, Neil S, Kulkarni H, Wright E, Agan BK, Marconi VC, Dolan MJ, Weiss RA & Ahuja SK

(2008) Duffy antigen receptor for chemokines mediates trans-infection of HIV-1 from red blood cells to target cells and affects HIV-AIDS susceptibility. *Cell Host Microbe* **4**, 52–62.
175 Horne KC, Li X, Jacobson LP, Palella F, Jamieson BD, Margolick JB, Martinson J, Turkozu V, Visvanathan K & Woolley IJ (2009) Duffy antigen polymorphisms do not alter progression of HIV in African Americans in the MACS cohort. *Cell Host Microbe* **5**, 415–417.
176 Julg B, Reddy S, van der Stok M, Kulkarni S, Qi Y, Bass S, Gold B, Nalls MA, Nelson GW, Walker BD *et al*. (2009) Lack of Duffy antigen receptor for chemokines: no influence on HIV disease progression in an African treatment-naive population. *Cell Host Microbe* **5**, 413–415.
177 Walley NM, Julg B, Dickson SP, Fellay J, Ge D, Walker BD, Carrington M, Cohen MS, de Bakker PIW, Goldstein DB *et al*. (2009) The Duffy antigen receptor for chemokines null promoter variant does not influence HIV-1 acquisition or disease progression. *Cell Host Microbe* **5**, 408–410.
178 Winkler CA, An P, Johnson R, Nelson GW & Kirk G (2009) Expression of Duffy antigen receptor for chemokines (DARC) has no effect on HIV-1 acquisition or progression to AIDS in African Americans. *Cell Host Microbe* **5**, 411–413.
179 Weber M, Blair E, Simpson CV, O'Hara M, Blackburn PE, Rot A, Graham GJ & Nibbs RJB (2004) The chemokine receptor D6 constitutively traffics to and from the cell surface to internalize and degrade chemokines. *Mol Biol Cell* **15**, 2492–2508.
180 Fra AM, Locati M, Otero K, Sironi M, Signorelli P, Massardi ML, Gobbi M, Vecchi A, Sozzani S & Mantovani A (2003) Cutting edge: scavenging of inflammatory CC chemokines by the promiscuous putatively silent chemokine receptor D6. *J Immunol* **170**, 2279–2282.
181 Nibbs RJ, Kriehuber E, Ponath PD, Parent D, Qin S, Campbell JD, Henderson A, Kerjaschki D, Maurer D, Graham GJ *et al*. (2001) The beta-chemokine receptor D6 is expressed by lymphatic endothelium and a subset of vascular tumors. *Am J Pathol* **158**, 867–877.
182 Madigan J, Freeman DJ, Menzies F, Forrow S, Nelson SM, Young A, Sharkey A, Moffett A, Graham GJ, Greer IA *et al*. (2010) Chemokine scavenger D6 is expressed by trophoblasts and AIDS the survival of mouse embryos transferred into allogeneic recipients. *J Immunol* **184**, 3202–3212.
183 Martinez de la Torre Y, Buracchi C, Borroni EM, Dupor J, Bonecchi R, Nebuloni M, Pasqualini F, Doni A, Lauri E, Agostinis C *et al*. (2007) Protection against inflammation- and autoantibody-caused fetal loss by the chemokine decoy receptor D6. *Proc Natl Acad Sci USA* **104**, 2319–2324.
184 Teoh PJ, Menzies FM, Hansell CAH, Clarke M, Waddell C, Burton GJ, Nelson SM & Nibbs RJB (2014) Atypical chemokine receptor ACKR2 mediates chemokine scavenging by primary human trophoblasts and can regulate fetal growth, placental structure, and neonatal mortality in mice. *J Immunol* **193**, 5218–5228.
185 Lee KM, Danuser R, Stein JV, Graham D, Nibbs RJ & Graham GJ (2014) The chemokine receptors ACKR2 and CCR2 reciprocally regulate lymphatic vessel density. *EMBO J* **33**, 2564–2580.
186 Lee KM, McKimmie CS, Gilchrist DS, Pallas KJ, Nibbs RJ, Garside P, McDonald V, Jenkins C, Ransohoff R, Liu L *et al*. (2011) D6 facilitates cellular migration, and fluid flow, to lymph nodes by suppressing lymphatic congestion. *Blood* **118**, 6220–6229.
187 Jamieson T, Cook DN, Nibbs RJB, Rot A, Nixon C, McLean P, Alcami A, Lira SA, Wiekowski M & Graham GJ (2005) The chemokine receptor D6 limits the inflammatory response in vivo. *Nat Immunol* **6**, 403–411.
188 Nibbs RJB, Gilchrist DS, King V, Ferra A, Forrow S, Hunter KD & Graham GJ (2007) The atypical chemokine receptor D6 suppresses the development of chemically induced skin tumors. *J Clin Invest* **117**, 1884–1892.
189 Hansell CAH, Schiering C, Kinstrie R, Ford L, Bordon Y, McInnes IB, Goodyear CS & Nibbs RJB (2011) Universal expression and dual function of the atypical chemokine receptor D6 on innate-like B cells in mice. *Blood* **117**, 5413–5424.
190 Wilson GJ, Hewit KD, Pallas KJ, Cairney CJ, Lee KM, Hansell CA, Stein T & Graham GJ (2017) Atypical chemokine receptor ACKR2 controls branching morphogenesis in the developing mammary gland. *Development* **144**, 74–82.
191 Dambly-Chaudière C, Cubedo N & Ghysen A (2007) Control of cell migration in the development of the posterior lateral line: antagonistic interactions between the chemokine receptors CXCR4 and CXCR7/RDC1. *BMC Dev Biol* **7**, 23.
192 Boldajipour B, Mahabaleshwar H, Kardash E, Reichman-Fried M, Blaser H, Minina S, Wilson D, Xu Q & Raz E (2008) Control of chemokine-guided cell migration by ligand sequestration. *Cell* **132**, 463–473.
193 Gerrits H, van Ingen Schenau DS, Bakker NEC, van Disseldorp AJM, Strik A, Hermens LS, Koenen TB, Krajnc-Franken MAM & Gossen JA (2008) Early postnatal lethality and cardiovascular defects in CXCR7-deficient mice. *Genesis* **46**, 235–245.
194 Yu S, Crawford D, Tsuchihashi T, Behrens TW & Srivastava D (2011) The chemokine receptor CXCR7 functions to regulate cardiac valve remodeling. *Dev Dyn* **240**, 384–393.
195 Sánchez-Alcañiz JA, Haege S, Mueller W, Pla R, Mackay F, Schulz S, López-Bendito G, Stumm R &

Marín O (2011) Cxcr7 controls neuronal migration by regulating chemokine responsiveness. *Neuron* **69**, 77–90.
196 Wang Y, Li G, Stanco A, Long JE, Crawford D, Potter GB, Pleasure SJ, Behrens T & Rubenstein JLR (2011) CXCR4 and CXCR7 have distinct functions in regulating interneuron migration. *Neuron* **69**, 61–76.
197 Haege S, Einer C, Thiele S, Mueller W, Nietzsche S, Lupp A, Mackay F, Schulz S & Stumm R (2012) CXC chemokine receptor 7 (CXCR7) regulates CXCR4 protein expression and capillary tuft development in mouse kidney. *PLoS ONE* **7**, e42814.
198 Cubedo N, Cerdan E, Sapède D & Rossel M (2009) CXCR4 and CXCR7 cooperate during tangential migration of facial motoneurons. *Mol Cell Neurosci* **40**, 474–484.
199 Zhu B, Xu D, Deng X, Chen Q, Huang Y, Peng H, Li Y, Jia B, Thoreson WB, Ding W *et al*. (2012) CXCL12 enhances human neural progenitor cell survival through a CXCR7- and CXCR4- mediated endocytotic signaling pathway. *Stem Cells* **30**, 2571–2583.
200 Valentin G, Haas P & Gilmour D (2007) The chemokine SDF1a coordinates tissue migration through the spatially restricted activation of Cxcr7 and Cxcr4b. *Curr Biol* **17**, 1026–1031.
201 Ulvmar MH, Werth K, Braun A, Kelay P, Hub E, Eller K, Chan L, Lucas B, Novitzky-Basso I, Nakamura K *et al*. (2014) The atypical chemokine receptor CCRL1 shapes functional CCL21 gradients in lymph nodes. *Nat Immunol* **15**, 623–630.
202 Bryce SA, Wilson RAM, Tiplady EM, Asquith DL, Bromley SK, Luster AD, Graham GJ & Nibbs RJB (2016) ACKR4 on stromal cells scavenges CCL19 To enable CCR7-dependent trafficking of APCs from inflamed skin to lymph nodes. *J Immunol* **196**, 3341–3353.
203 Comerford I, Milasta S, Morrow V, Milligan G & Nibbs R (2006) The chemokine receptor CCX-CKR mediates effective scavenging of CCL19 in vitro. *Eur J Immunol* **36**, 1904–1916.
204 Comerford I, Nibbs RJ, Litchfield W, Bunting M, Harata-Lee Y, Haylock-Jacobs S, Forrow S, Körner H & McColl SR (2010) The atypical chemokine receptor CCX-CKR scavenges homeostatic chemokines in circulation and tissues and suppresses Th17 responses. *Blood* **116**, 4130–4140.
205 Bunting MD, Comerford I, Seach N, Hammett MV, Asquith DL, Körner H, Boyd RL, Nibbs RJB & McColl SR (2013) CCX-CKR deficiency alters thymic stroma impairing thymocyte development and promoting autoimmunity. *Blood* **121**, 118–128.
206 Lucas B, White AJ, Ulvmar MH, Nibbs RJB, Sitnik KM, Agace WW, Jenkinson WE, Anderson G & Rot A (2015) CCRL1/ACKR4 is expressed in key thymic microenvironments but is dispensable for T lymphopoiesis at steady state in adult mice. *Eur J Immunol* **45**, 574–583.
207 Cardona AE, Sasse ME, Liu L, Cardona SM, Mizutani M, Savarin C, Hu T & Ransohoff RM (2008) Scavenging roles of chemokine receptors: chemokine receptor deficiency is associated with increased levels of ligand in circulation and tissues. *Blood* **112**, 256–263.
208 López-Cotarelo P, Gómez-Moreira C, Criado-García O, Sánchez L & Rodríguez-Fernández JL (2017) Beyond chemoattraction: multifunctionality of chemokine receptors in leukocytes. *Trends Immunol* **38**, 927–941.
209 Wolf M & Moser B (2012) Antimicrobial activities of chemokines: not just a side-effect? *Front Immunol* **3**, 213.
210 Kulkarni N, Pathak M & Lal G (2017) Role of chemokine receptors and intestinal epithelial cells in the mucosal inflammation and tolerance. *J Leukoc Biol* **101**, 377–394.
211 Beck LA, Tancowny B, Brummet ME, Asaki SY, Curry SL, Penno MB, Foster M, Bahl A & Stellato C (2006) Functional analysis of the chemokine receptor CCR3 on airway epithelial cells. *J Immunol* **177**, 3344–3354.
212 Ghosh MC, Makena PS, Gorantla VK, Sinclair SE & Waters CM (2012) CXCR4 regulates migration of lung alveolar epithelial cells through activation of Rac1 and Matrix Metalloproteinase-2 (MMP-2). *Am J Physiol Lung Cell Mol Physiol* **302**, L846–856.
213 Cartier L, Hartley O, Dubois-Dauphin M & Krause K-H (2005) Chemokine receptors in the central nervous system: role in brain inflammation and neurodegenerative diseases. *Brain Res Brain Res Rev* **48**, 16–42.
214 Dimberg A (2010) Chemokines in angiogenesis. *Curr Top Microbiol Immunol* **341**, 59–80.
215 Mehrad B, Keane MP & Strieter RM (2007) Chemokines as mediators of angiogenesis. *Thromb Haemost* **97**, 755–762.
216 Chamberlain G, Wright K, Rot A, Ashton B & Middleton J (2008) Murine mesenchymal stem cells exhibit a restricted repertoire of functional chemokine receptors: comparison with human. *PLoS ONE* **3**, e2934.
217 Zlotnik A, Burkhardt AM & Homey B (2011) Homeostatic chemokine receptors and organ-specific metastasis. *Nat Rev Immunol* **11**, 597–606.
218 Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN *et al*. (2001) Involvement of chemokine receptors in breast cancer metastasis. *Nature* **410**, 50–56.
219 Bussmann J & Raz E (2015) Chemokine-guided cell migration and motility in zebrafish development. *EMBO J* **34**, 1309–1318.
220 Donà E, Barry JD, Valentin G, Quirin C, Khmelinskii A, Kunze A, Durdu S, Newton LR, Fernandez-Minan A, Huber W *et al*. (2013) Directional tissue migration

through a self-generated chemokine gradient. *Nature* **503**, 285–289.
221 Malet-Engra G, Yu W, Oldani A, Rey-Barroso J, Gov NS, Scita G & Dupré L (2015) Collective cell motility promotes chemotactic prowess and resistance to chemorepulsion. *Curr Biol* **25**, 242–250.
222 Tharp WG, Yadav R, Irimia D, Upadhyaya A, Samadani A, Hurtado O, Liu S-Y, Munisamy S, Brainard DM, Mahon MJ *et al.* (2006) Neutrophil chemorepulsion in defined interleukin-8 gradients in vitro and in vivo. *J Leukoc Biol* **79**, 539–554.
223 Poznansky MC, Olszak IT, Foxall R, Evans RH, Luster AD & Scadden DT (2000) Active movement of T cells away from a chemokine. *Nat Med* **6**, 543–548.
224 Poznansky MC, Olszak IT, Evans RH, Wang Z, Foxall RB, Olson DP, Weibrecht K, Luster AD & Scadden DT (2002) Thymocyte emigration is mediated by active movement away from stroma-derived factors. *J Clin Invest* **109**, 1101–1110.
225 Weninger W, Biro M & Jain R (2014) Leukocyte migration in the interstitial space of non-lymphoid organs. *Nat Rev Immunol* **14**, 232–246.
226 Kara EE, Bastow CR, McKenzie DR, Gregor CE, Fenix KA, Babb R, Norton TS, Zotos D, Rodda LB, Hermes JR *et al.* (2018) Atypical chemokine receptor 4 shapes activated B cell fate. *J Exp Med* **215**, 801–813.
227 Kunkel EJ, Campbell JJ, Haraldsen G, Pan J, Boisvert J, Roberts AI, Ebert EC, Vierra MA, Goodman SB, Genovese MC *et al.* (2000) Lymphocyte CC chemokine receptor 9 and epithelial thymus-expressed chemokine (TECK) expression distinguish the small intestinal immune compartment: Epithelial expression of tissue-specific chemokines as an organizing principle in regional immunity. *J Exp Med* **192**, 761–768.
228 Schaerli P, Willimann K, Ebert LM, Walz A & Moser B (2005) Cutaneous CXCL14 targets blood precursors to epidermal niches for Langerhans cell differentiation. *Immunity* **23**, 331–342.
229 Homey B, Alenius H, Müller A, Soto H, Bowman EP, Yuan W, McEvoy L, Lauerma AI, Assmann T, Bünemann E *et al.* (2002) CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* **8**, 157–165.
230 Nagasawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, Yoshida N, Kikutani H & Kishimoto T (1996) Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature* **382**, 635–638.
231 Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, Kitamura Y, Matsushima K, Yoshida N, Nishikawa S *et al.* (1998) The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. *Nature* **393**, 591–594.
232 Zou YR, Kottmann AH, Kuroda M, Taniuchi I & Littman DR (1998) Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature* **393**, 595–599.
233 Klein KR, Karpinich NO, Espenschied ST, Willcockson HH, Dunworth WP, Hoopes SL, Kushner EJ, Bautch VL & Caron KM (2014) Decoy receptor CXCR7 modulates adrenomedullin-mediated cardiac and lymphatic vascular development. *Dev Cell* **30**, 528–540.
234 Sugiyama T, Kohara H, Noda M & Nagasawa T (2006) Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. *Immunity* **25**, 977–988.
235 Nie Y, Han Y-C & Zou Y-R (2008) CXCR4 is required for the quiescence of primitive hematopoietic cells. *J Exp Med* **205**, 777–783.
236 Lim VY, Zehentmeier S, Fistonich C & Pereira JP (2017) A chemoattractant-guided walk through lymphopoiesis: from hematopoietic stem cells to mature B lymphocytes. *Adv Immunol* **134**, 47–88.
237 Bilgin YM & de Greef GE (2016) Plerixafor for stem cell mobilization: the current status. *Curr Opin Hematol* **23**, 67–71.
238 Hernandez PA, Gorlin RJ, Lukens JN, Taniuchi S, Bohinjec J, Francois F, Klotman ME & Diaz GA (2003) Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* **34**, 70–74.
239 Liu Q, Chen H, Ojode T, Gao X, Anaya-O'Brien S, Turner NA, Ulrick J, Decastro R, Kelly C, Cardones AR *et al.* (2012) WHIM syndrome caused by a single amino acid substitution in the carboxy-tail of chemokine receptor CXCR4. *Blood* **120**, 181–189.
240 Balabanian K, Lagane B, Pablos JL, Laurent L, Planchenault T, Verola O, Lebbe C, Kerob D, Dupuy A, Hermine O *et al.* (2005) WHIM syndromes with different genetic anomalies are accounted for by impaired CXCR4 desensitization to CXCL12. *Blood* **105**, 2449–2457.
241 Gulino AV, Moratto D, Sozzani S, Cavadini P, Otero K, Tassone L, Imberti L, Pirovano S, Notarangelo LD, Soresina R *et al.* (2004) Altered leukocyte response to CXCL12 in patients with warts hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome. *Blood* **104**, 444–452.
242 McDermott DH, Liu Q, Velez D, Lopez L, Anaya-O'Brien S, Ulrick J, Kwatemaa N, Starling J, Fleisher TA, Priel DAL *et al.* (2014) A phase 1 clinical trial of long-term, low-dose treatment of WHIM syndrome with the CXCR4 antagonist plerixafor. *Blood* **123**, 2308–2316.
243 McDermott DH, Gao J-L, Liu Q, Siwicki M, Martens C, Jacobs P, Velez D, Yim E, Bryke CR, Hsu N *et al.*

(2015) Chromothriptic cure of WHIM syndrome. *Cell* **160**, 686–699.
244 Förster R, Mattis AE, Kremmer E, Wolf E, Brem G & Lipp M (1996) A putative chemokine receptor, BLR1, directs B cell migration to defined lymphoid organs and specific anatomic compartments of the spleen. *Cell* **87**, 1037–1047.
245 Ansel KM, Ngo VN, Hyman PL, Luther SA, Förster R, Sedgwick JD, Browning JL, Lipp M & Cyster JG (2000) A chemokine-driven positive feedback loop organizes lymphoid follicles. *Nature* **406**, 309–314.
246 Finke D, Acha-Orbea H, Mattis A, Lipp M & Kraehenbuhl J (2002) CD4+CD3- cells induce Peyer's patch development: role of alpha4beta1 integrin activation by CXCR5. *Immunity* **17**, 363–373.
247 Ohl L, Henning G, Krautwald S, Lipp M, Hardtke S, Bernhardt G, Pabst O & Förster R (2003) Cooperating mechanisms of CXCR5 and CCR7 in development and organization of secondary lymphoid organs. *J Exp Med* **197**, 1199–1204.
248 Luther SA, Ansel KM & Cyster JG (2003) Overlapping roles of CXCL13, interleukin 7 receptor alpha, and CCR7 ligands in lymph node development. *J Exp Med* **197**, 1191–1198.
249 de Pavert SAV, Olivier BJ, Goverse G, Vondenhoff MF, Greuter M, Beke P, Kusser K, Höpken UE, Lipp M, Niederreither K *et al.* (2009) Chemokine CXCL13 is essential for lymph node initiation and is induced by retinoic acid and neuronal stimulation. *Nat Immunol* **10**, 1193–1199.
250 Ueno T, Hara K, Willis MS, Malin MA, Höpken UE, Gray DHD, Matsushima K, Lipp M, Springer TA, Boyd RL *et al.* (2002) Role for CCR7 ligands in the emigration of newly generated T lymphocytes from the neonatal thymus. *Immunity* **16**, 205–218.
251 Kwan J & Killeen N (2004) CCR7 directs the migration of thymocytes into the thymic medulla. *J Immunol* **172**, 3999–4007.
252 Kurobe H, Liu C, Ueno T, Saito F, Ohigashi I, Seach N, Arakaki R, Hayashi Y, Kitagawa T, Lipp M *et al.* (2006) CCR7-dependent cortex-to-medulla migration of positively selected thymocytes is essential for establishing central tolerance. *Immunity* **24**, 165–177.
253 Ueno T, Saito F, Gray DHD, Kuse S, Hieshima K, Nakano H, Kakiuchi T, Lipp M, Boyd RL & Takahama Y (2004) CCR7 signals are essential for cortex-medulla migration of developing thymocytes. *J Exp Med* **200**, 493–505.
254 Misslitz A, Pabst O, Hintzen G, Ohl L, Kremmer E, Petrie HT & Förster R (2004) Thymic T cell development and progenitor localization depend on CCR7. *J Exp Med* **200**, 481–491.
255 Davalos-Misslitz ACM, Rieckenberg J, Willenzon S, Worbs T, Kremmer E, Bernhardt G & Förster R (2007) Generalized multi-organ autoimmunity in CCR7-deficient mice. *Eur J Immunol* **37**, 613–622.
256 Hu Z, Lancaster JN, Sasiponganan C & Ehrlich LIR (2015) CCR4 promotes medullary entry and thymocyte-dendritic cell interactions required for central tolerance. *J Exp Med* **212**, 1947–1965.
257 Cowan JE, McCarthy NI, Parnell SM, White AJ, Bacon A, Serge A, Irla M, Lane PJL, Jenkinson EJ, Jenkinson WE *et al.* (2014) Differential requirement for CCR4 and CCR7 during the development of innate and adaptive αβT cells in the adult thymus. *J Immunol* **193**, 1204–1212.
258 Wurbel MA, Malissen M, Guy-Grand D, Meffre E, Nussenzweig MC, Richelme M, Carrier A & Malissen B (2001) Mice lacking the CCR9 CC-chemokine receptor show a mild impairment of early T- and B-cell development and a reduction in T-cell receptor gammadelta(+) gut intraepithelial lymphocytes. *Blood* **98**, 2626–2632.
259 Hu Z, Li Y, Van Nieuwenhuijze A, Selden HJ, Jarrett AM, Sorace AG, Yankeelov TE, Liston A & Ehrlich LIR (2017) CCR7 modulates the generation of thymic regulatory T cells by altering the composition of the thymic dendritic cell compartment. *Cell Rep* **21**, 168–180.
260 Lancaster JN, Li Y & Ehrlich LIR (2018) Chemokine-mediated choreography of thymocyte development and selection. *Trends Immunol* **39**, 86–98.
261 Kozai M, Kubo Y, Katakai T, Kondo H, Kiyonari H, Schaeuble K, Luther SA, Ishimaru N, Ohigashi I & Takahama Y (2017) Essential role of CCL21 in establishment of central self-tolerance in T cells. *J Exp Med* **214**, 1925–1935.
262 Förster R, Davalos-Misslitz AC & Rot A (2008) CCR7 and its ligands: balancing immunity and tolerance. *Nat Rev Immunol* **8**, 362–371.
263 Druzd D, Matveeva O, Ince L, Harrison U, He W, Schmal C, Herzel H, Tsang AH, Kawakami N, Leliavski A *et al.* (2017) Lymphocyte circadian clocks control lymph node trafficking and adaptive immune responses. *Immunity* **46**, 120–132.
264 Nakai A, Hayano Y, Furuta F, Noda M & Suzuki K (2014) Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. *J Exp Med* **211**, 2583–2598.
265 Suzuki K, Hayano Y, Nakai A, Furuta F & Noda M (2016) Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. *J Exp Med* **213**, 2567–2574.
266 Förster R, Schubel A, Breitfeld D, Kremmer E, Renner-Müller I, Wolf E & Lipp M (1999) CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. *Cell* **99**, 23–33.

267 Okada T & Cyster JG (2007) CC chemokine receptor 7 contributes to Gi-dependent T cell motility in the lymph node. *J Immunol* **178**, 2973–2978.
268 Worbs T, Mempel TR, Bölter J, von Andrian UH & Förster R (2007) CCR7 ligands stimulate the intranodal motility of T lymphocytes in vivo. *J Exp Med* **204**, 489–495.
269 Woolf E, Grigorova I, Sagiv A, Grabovsky V, Feigelson SW, Shulman Z, Hartmann T, Sixt M, Cyster JG & Alon R (2007) Lymph node chemokines promote sustained T lymphocyte motility without triggering stable integrin adhesiveness in the absence of shear forces. *Nat Immunol* **8**, 1076–1085.
270 Pham THM, Okada T, Matloubian M, Lo CG & Cyster JG (2008) S1P1 receptor signaling overrides retention mediated by G alpha i-coupled receptors to promote T cell egress. *Immunity* **28**, 122–133.
271 Debes GF, Arnold CN, Young AJ, Krautwald S, Lipp M, Hay JB & Butcher EC (2005) Chemokine receptor CCR7 required for T lymphocyte exit from peripheral tissues. *Nat Immunol* **6**, 889–894.
272 Bromley SK, Thomas SY & Luster AD (2005) Chemokine receptor CCR7 guides T cell exit from peripheral tissues and entry into afferent lymphatics. *Nat Immunol* **6**, 895–901.
273 Vaahtomeri K, Brown M, Hauschild R, de Vries I, Leithner AF, Mehling M, Kaufmann WA & Sixt M (2017) Locally triggered release of the chemokine CCL21 promotes dendritic cell transmigration across lymphatic endothelia. *Cell Rep* **19**, 902–909.
274 Tal O, Lim HY, Gurevich I, Milo I, Shipony Z, Ng LG, Angeli V & Shakhar G (2011) DC mobilization from the skin requires docking to immobilized CCL21 on lymphatic endothelium and intralymphatic crawling. *J Exp Med* **208**, 2141–2153.
275 Russo E, Teijeira A, Vaahtomeri K, Willrodt A-H, Bloch JS, Nitschké M, Santambrogio L, Kerjaschki D, Sixt M & Halin C (2016) Intralymphatic CCL21 promotes tissue egress of dendritic cells through afferent lymphatic vessels. *Cell Rep* **14**, 1723–1734.
276 Braun A, Worbs T, Moschovakis GL, Halle S, Hoffmann K, Bölter J, Münk A & Förster R (2011) Afferent lymph-derived T cells and DCs use different chemokine receptor CCR7-dependent routes for entry into the lymph node and intranodal migration. *Nat Immunol* **15**, 623–630.
277 Serbina NV & Pamer EG (2006) Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2. *Nat Immunol* **7**, 311–317.
278 Humbles AA, Lu B, Friend DS, Okinaga S, Lora J, Al-Garawi A, Martin TR, Gerard NP & Gerard C (2002) The murine CCR3 receptor regulates both the role of eosinophils and mast cells in allergen-induced airway inflammation and hyperresponsiveness. *Proc Natl Acad Sci USA* **99**, 1479–1484.
279 Eash KJ, Greenbaum AM, Gopalan PK & Link DC (2010) CXCR2 and CXCR4 antagonistically regulate neutrophil trafficking from murine bone marrow. *J Clin Invest* **120**, 2423–2431.
280 Martin C, Burdon PCE, Bridger G, Gutierrez-Ramos JC, Williams TJ & Rankin SM (2003) Chemokines acting via CXCR2 and CXCR4 control the release of neutrophils from the bone marrow and their return following senescence. *Immunity* **19**, 583–593.
281 Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, Sarnacki S, Cumano A, Lauvau G & Geissmann F (2007) Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science* **317**, 666–670.
282 Wendland M, Czeloth N, Mach N, Malissen B, Kremmer E, Pabst O & Förster R (2007) CCR9 is a homing receptor for plasmacytoid dendritic cells to the small intestine. *Proc Natl Acad Sci USA* **104**, 6347–6352.
283 Cinamon G, Zachariah MA, Lam OM, Foss FW & Cyster JG (2008) Follicular shuttling of marginal zone B cells facilitates antigen transport. *Nat Immunol* **9**, 54–62.
284 Ansel KM, Harris RBS & Cyster JG (2002) CXCL13 is required for B1 cell homing, natural antibody production, and body cavity immunity. *Immunity* **16**, 67–76.
285 Griffith JW, Sokol CL & Luster AD (2014) Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu Rev Immunol* **32**, 659–702.
286 Lim K, Hyun Y-M, Lambert-Emo K, Capece T, Bae S, Miller R, Topham DJ & Kim M (2015) Neutrophil trails guide influenza-specific $CD8^+$ T cells in the airways. *Science* **349**, aaa4352.
287 Thanabalasuriar A, Neupane AS, Wang J, Krummel MF & Kubes P (2016) iNKT cell emigration out of the lung vasculature requires neutrophils and monocyte-derived dendritic cells in inflammation. *Cell Rep* **16**, 3260–3272.
288 Asquith DL, Bryce SA & Nibbs RJB (2015) Targeting cell migration in rheumatoid arthritis. *Curr Opin Rheumatol* **27**, 204–211.
289 Cheng W & Chen G (2014) Chemokines and chemokine receptors in multiple sclerosis. *Mediators Inflamm* **2014**, 659206.
290 Singh TP, Lee CH & Farber JM (2013) Chemokine receptors in psoriasis. *Expert Opin Ther Targets* **17**, 1405–1422.
291 Castan L, Magnan A & Bouchaud G (2017) Chemokine receptors in allergic diseases. *Allergy* **72**, 682–690.

292 Le Thuc O, Blondeau N, Nahon J-L & Rovère C (2015) The complex contribution of chemokines to neuroinflammation: switching from beneficial to detrimental effects. *Ann N Y Acad Sci* **1351**, 127–140.
293 Nishimura M, Kuboi Y, Muramoto K, Kawano T & Imai T (2009) Chemokines as novel therapeutic targets for inflammatory bowel disease. *Ann N Y Acad Sci* **1173**, 350–356.
294 van der Vorst EPC, Döring Y & Weber C (2015) Chemokines. *Arteriosclero Thromb Vasc Biol* **35**, e52–e56.
295 Nagarsheth N, Wicha MS & Zou W (2017) Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol* **17**, 559–572.
296 Schall TJ & Proudfoot AEI (2011) Overcoming hurdles in developing successful drugs targeting chemokine receptors. *Nat Rev Immunol* **11**, 355–363.
297 Dieu MC, Vanbervliet B, Vicari A, Bridon JM, Oldham E, Aït-Yahia S, Briere F, Zlotnik A, Lebecque S & Caux C (1998) Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. *J Exp Med* **188**, 373–386.
298 Sozzani S, Allavena P, D'Amico G, Luini W, Bianchi G, Kataura M, Imai T, Yoshie O, Bonecchi R & Mantovani A (1998) Differential regulation of chemokine receptors during dendritic cell maturation: a model for their trafficking properties. *J Immunol* **161**, 1083–1086.
299 Sallusto F, Schaerli P, Loetscher P, Schaniel C, Lenig D, Mackay CR, Qin S & Lanzavecchia A (1998) Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. *Eur J Immunol* **28**, 2760–2769.
300 Molon B, Gri G, Bettella M, Gómez-Moutón C, Lanzavecchia A, Martínez-A C, Mañes S & Viola A (2005) T cell costimulation by chemokine receptors. *Nat Immunol* **6**, 465–471.
301 Contento RL, Molon B, Boularan C, Pozzan T, Mañes S, Marullo S & Viola A (2008) CXCR4-CCR5: a couple modulating T cell functions. *Proc Natl Acad Sci USA* **105**, 10101–10106.
302 Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, Parente E, Filì L, Ferri S, Frosali F *et al.* (2007) Phenotypic and functional features of human Th17 cells. *J Exp Med* **204**, 1849–1861.
303 Singh SP, Zhang HH, Foley JF, Hedrick MN & Farber JM (2008) Human T cells that are able to produce IL-17 express the chemokine receptor CCR6. *J Immunol* **180**, 214–221.
304 Sallusto F, Mackay CR & Lanzavecchia A (1997) Selective expression of the eotaxin receptor CCR3 by human T helper 2 cells. *Science* **277**, 2005–2007.
305 Bonecchi R, Bianchi G, Bordignon PP, D'Ambrosio D, Lang R, Borsatti A, Sozzani S, Allavena P, Gray PA, Mantovani A *et al.* (1998) Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. *J Exp Med* **187**, 129–134.
306 Loetscher P, Uguccioni M, Bordoli L, Baggiolini M, Moser B, Chizzolini C & Dayer JM (1998) CCR5 is characteristic of Th1 lymphocytes. *Nature* **391**, 344–345.
307 Sallusto F, Lenig D, Mackay CR & Lanzavecchia A (1998) Flexible programs of chemokine receptor expression on human polarized T helper 1 and 2 lymphocytes. *J Exp Med* **187**, 875–883.
308 Kim CH, Rott L, Kunkel EJ, Genovese MC, Andrew DP, Wu L & Butcher EC (2001) Rules of chemokine receptor association with T cell polarization in vivo. *J Clin Invest* **108**, 1331–1339.
309 Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M & Förster R (2000) Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J Exp Med* **192**, 1545–1552.
310 Schaerli P, Willimann K, Lang AB, Lipp M, Loetscher P & Moser B (2000) CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. *J Exp Med* **192**, 1553–1562.
311 Kim CH, Rott LS, Clark-Lewis I, Campbell DJ, Wu L & Butcher EC (2001) Subspecialization of CXCR5+ T cells: B helper activity is focused in a germinal center-localized subset of CXCR5+ T cells. *J Exp Med* **193**, 1373–1381.
312 Vaeth M, Müller G, Stauss D, Dietz L, Klein-Hessling S, Serfling E, Lipp M, Berberich I & Berberich-Siebelt F (2014) Follicular regulatory T cells control humoral autoimmunity via NFAT2-regulated CXCR5 expression. *J Exp Med* **211**, 545–561.
313 Vinuesa CG, Linterman MA, Yu D & MacLennan ICM (2016) Follicular helper T cells. *Annu Rev Immunol* **34**, 335–368.
314 Sage PT & Sharpe AH (2016) T follicular regulatory cells. *Immunol Rev* **271**, 246–259.
315 Leong YA, Chen Y, Ong HS, Wu D, Man K, Deleage C, Minnich M, Meckiff BJ, Wei Y, Hou Z *et al.* (2016) CXCR5(+) follicular cytotoxic T cells control viral infection in B cell follicles. *Nat Immunol* **17**, 1187–1196.
316 Svensson M, Marsal J, Ericsson A, Carramolino L, Brodén T, Márquez G & Agace WW (2002) CCL25 mediates the localization of recently activated CD8alphabeta(+) lymphocytes to the small-intestinal mucosa. *J Clin Invest* **110**, 1113–1121.
317 Stenstad H, Ericsson A, Johansson-Lindbom B, Svensson M, Marsal J, Mack M, Picarella D, Soler D, Márquez G, Briskin M *et al.* (2006) Gut-associated

lymphoid tissue-primed CD4+ T cells display CCR9-dependent and -independent homing to the small intestine. *Blood* **107**, 3447–3454.
318 Stenstad H, Svensson M, Cucak H, Kotarsky K & Agace WW (2007) Differential homing mechanisms regulate regionalized effector CD8alphabeta+ T cell accumulation within the small intestine. *Proc Natl Acad Sci USA* **104**, 10122–10127.
319 Johansson-Lindbom B & Agace WW (2007) Generation of gut-homing T cells and their localization to the small intestinal mucosa. *Immunol Rev* **215**, 226–242.
320 Mora JR, Bono MR, Manjunath N, Weninger W, Cavanagh LL, Rosemblatt M & von Andrian UH (2003) Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature* **424**, 88–93.
321 Johansson-Lindbom B, Svensson M, Wurbel M-A, Malissen B, Márquez G & Agace W (2003) Selective generation of gut tropic T cells in gut-associated lymphoid tissue (GALT): requirement for GALT dendritic cells and adjuvant. *J Exp Med* **198**, 963–969.
322 Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C & Song S-Y (2004) Retinoic acid imprints gut-homing specificity on T cells. *Immunity* **21**, 527–538.
323 Johansson-Lindbom B, Svensson M, Pabst O, Palmqvist C, Márquez G, Förster R & Agace WW (2005) Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing. *J Exp Med* **202**, 1063–1073.
324 Hammerschmidt SI, Ahrendt M, Bode U, Wahl B, Kremmer E, Förster R & Pabst O (2008) Stromal mesenteric lymph node cells are essential for the generation of gut-homing T cells in vivo. *J Exp Med* **205**, 2483–2490.
325 Reiss Y, Proudfoot AE, Power CA, Campbell JJ & Butcher EC (2001) CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. *J Exp Med* **194**, 1541–1547.
326 Kunkel EJ & Butcher EC (2002) Chemokines and the tissue-specific migration of lymphocytes. *Immunity* **16**, 1–4.
327 Schaerli P, Ebert L, Willimann K, Blaser A, Roos RS, Loetscher P & Moser B (2004) A skin-selective homing mechanism for human immune surveillance T cells. *J Exp Med* **199**, 1265–1275.
328 Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D & Butcher EC (2007) DCs metabolize sunlight-induced vitamin D3 to "program" T cell attraction to the epidermal chemokine CCL27. *Nat Immunol* **8**, 285–293.
329 McCully ML, Ladell K, Hakobyan S, Mansel RE, Price DA & Moser B (2012) Epidermis instructs skin homing receptor expression in human T cells. *Blood* **120**, 4591–4598.
330 Sallusto F, Lenig D, Förster R, Lipp M & Lanzavecchia A (1999) Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. *Nature* **401**, 708–712.
331 Gerlach C, Moseman EA, Loughhead SM, Alvarez D, Zwijnenburg AJ, Waanders L, Garg R, de la Torre JC & von Andrian UH (2016) The chemokine receptor CX3CR1 defines three antigen-experienced CD8T cell subsets with distinct roles in immune surveillance and homeostasis. *Immunity* **45**, 1270–1284.
332 Reif K, Ekland EH, Ohl L, Nakano H, Lipp M, Förster R & Cyster JG (2002) Balanced responsiveness to chemoattractants from adjacent zones determines B-cell position. *Nature* **416**, 94–99.
333 Allen CDC, Ansel KM, Low C, Lesley R, Tamamura H, Fujii N & Cyster JG (2004) Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. *Nat Immunol* **5**, 943–952.
334 Allen CDC, Okada T & Cyster JG (2007) Germinal-center organization and cellular dynamics. *Immunity* **27**, 190–202.
335 Suan D, Kräutler NJ, Maag JLV, Butt D, Bourne K, Hermes JR, Avery DT, Young C, Statham A, Elliott M *et al.* (2017) CCR6 defines memory B cell precursors in mouse and human germinal centers, revealing light-zone location and predominant low antigen affinity. *Immunity* **47** (1142–1153), e4.
336 Hargreaves DC, Hyman PL, Lu TT, Ngo VN, Bidgol A, Suzuki G, Zou YR, Littman DR & Cyster JG (2001) A coordinated change in chemokine responsiveness guides plasma cell movements. *J Exp Med* **194**, 45–56.
337 Cyster JG (2003) Homing of antibody secreting cells. *Immunol Rev* **194**, 48–60.
338 Hu S, Yang K, Yang J, Li M & Xiong N (2011) Critical roles of chemokine receptor CCR10 in regulating memory IgA responses in intestines. *Proc Natl Acad Sci USA* **108**, E1035–E1044.
339 Pabst O, Ohl L, Wendland M, Wurbel M-A, Kremmer E, Malissen B & Förster R (2004) Chemokine receptor CCR9 contributes to the localization of plasma cells to the small intestine. *J Exp Med* **199**, 411–416.
340 Hieshima K, Kawasaki Y, Hanamoto H, Nakayama T, Nagakubo D, Kanamaru A & Yoshie O (2004) CC chemokine ligands 25 and 28 play essential roles in intestinal extravasation of IgA antibody-secreting cells. *J Immunol* **173**, 3668–3675.
341 Wilson E & Butcher EC (2004) CCL28 controls immunoglobulin (Ig)A plasma cell accumulation in the lactating mammary gland and IgA antibody transfer to the neonate. *J Exp Med* **200**, 805–809.
342 Morteau O, Gerard C, Lu B, Ghiran S, Rits M, Fujiwara Y, Law Y, Distelhorst K, Nielsen EM, Hill

ED *et al*. (2008) An indispensable role for the chemokine receptor CCR10 in IgA antibody-secreting cell accumulation. *J Immunol* **181**, 6309–6315.

343 Mora JR & von Andrian UH (2008) Differentiation and homing of IgA-secreting cells. *Mucosal Immunol* **1**, 96–109.

344 Collins PJ, McCully ML, Martínez-Muñoz L, Santiago C, Wheeldon J, Caucheteux S, Thelen S, Cecchinato V, Laufer JM, Purvanov V *et al*. (2017) Epithelial chemokine CXCL14 synergizes with CXCL12 via allosteric modulation of CXCR4. *FASEB J* **31**, 3084–3097.

345 Alampour-Rajabi S, El Bounkari O, Rot A, Müller-Newen G, Bachelerie F, Gawaz M, Weber C, Schober A & Bernhagen J (2015) MIF interacts with CXCR7 to promote receptor internalization, ERK1/2 and ZAP-70 signaling, and lymphocyte chemotaxis. *FASEB J* **29**, 4497–4511.

346 Smith N, Pietrancosta N, Davidson S, Dutrieux J, Chauveau L, Cutolo P, Dy M, Scott-Algara D, Manoury B, Zirafi O *et al*. (2017) Natural amines inhibit activation of human plasmacytoid dendritic cells through CXCR4 engagement. *Nat Commun* **8**, 14253.

347 Pei X, Sun Q, Zhang Y, Wang P, Peng X, Guo C, Xu E, Zheng Y, Mo X, Ma J *et al*. (2014) PC3-secreted microprotein is a novel chemoattractant protein and functions as a high-affinity ligand for CC chemokine receptor 2. *J Immunol* **192**, 1878–1886.

348 Ignatov A, Robert J, Gregory-Evans C & Schaller HC (2006) RANTES stimulates Ca2+ mobilization and inositol trisphosphate (IP3) formation in cells transfected with G protein-coupled receptor 75. *Br J Pharmacol* **149**, 490–497.

349 Makita S & Tobinai K (2017) Mogamulizumab for the treatment of T-cell lymphoma. *Expert Opin Biol Ther* **17**, 1145–1153.

350 Rot A & von Andrian UH (2004) Chemokines in innate and adaptive host defense: basic chemokinese grammar for immune cells. *Annu Rev Immunol* **22**, 891–928.

351 Heng TSP, Painter MW & Consortium IGP (2008) The Immunological Genome Project: networks of gene expression in immune cells. *Nat Immunol* **9**, 1091–1094.