

The Chemokine System in Innate Immunity

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Chemokines are chemotactic cytokines that control the migration and positioning of immune cells in tissues and are critical for the function of the innate immune system. Chemokines control the release of innate immune cells from the bone marrow during homeostasis as well as in response to infection and inflammation. They also recruit innate immune effectors out of the circulation and into the tissue where, in collaboration with other chemoattractants, they guide these cells to the very sites of tissue injury. Chemokine function is also critical for the positioning of innate immune sentinels in peripheral tissue and then, following innate immune activation, guiding these activated cells to the draining lymph node to initiate and imprint an adaptive immune response. In this review, we will highlight recent advances in understanding how chemokine function regulates the movement and positioning of innate immune cells at homeostasis and in response to acute inflammation, and then we will review how chemokine-mediated innate immune cell trafficking plays an essential role in linking the innate and adaptive immune responses.

Chemokines are chemotactic cytokines that control cell migration and cell positioning throughout development, homeostasis, and inflammation. The immune system, which is dependent on the coordinated migration of cells, is particularly dependent on chemokines for its function. Not only do chemokines guide immune effector cells to sites of infection or inflammation, but they also coordinate interactions between immune cells. By doing so, chemokines promote interactions between the innate and adaptive immune systems, thus shaping and providing the necessary context for the development of optimal adaptive immune responses. This review will aim to provide an overview of the function of the chemokine system,

with emphasis placed on its role in the innate immune system.

CHEMOKINES AND CHEMOKINE RECEPTORS

The chemokine family consists of ~50 endogenous chemokine ligands in humans and mice (Table 1). These small, 8- to 12-kDa protein ligands promote increased motility and directional migration when they bind to their corresponding cell-surface receptor. The chemokine ligands are divided into four groups based on the positioning of their initial cysteine residues: XC, CC, CXC, and CX3C. Thus, CC chemokine ligands (CCLs) have two

Editors: Ruslan M. Medzhitov

Additional Perspectives on Innate Immunity and Inflammation available at www.cshperspectives.org

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Cite this article as *Cold Spring Harb Perspect Biol* 2015;7:a016303

Table 1. Chemokines

Chemokine	Other names	Receptor	Key/main immune function
CXCL1	GRO- α , MGSA, mouse KC	CXCR2	Neutrophil trafficking
CXCL2	GRO- β , MIP-2 α , mouse MIP2	CXCR2	Neutrophil trafficking
CXCL3	GRO- γ , MIP-2 β	CXCR2	Neutrophil trafficking
CXCL4	PF4	?	Procoagulant
CXCL5	ENA-78, mouse LIX	CXCR2	Neutrophil trafficking
CXCL6	GCP-2	CXCR1, CXCR2	Neutrophil trafficking
CXCL7	NAP-2	CXCR2	Neutrophil trafficking
CXCL8	IL-8 (no mouse)	CXCR1, CXCR2	Neutrophil trafficking
CXCL9	Mig	CXCR3	Th1 response; Th1, CD8, NK trafficking
CXCL10	IP-10	CXCR3	Th1 response; Th1, CD8, NK trafficking
CXCL11	I-TAC	CXCR3	Th1 response; Th1, CD8, NK trafficking
CXCL12	SDF-1	CXCR4	Bone-marrow homing
CXCL13	BLC, BCA-1	CXCR5	B-cell and T _{FH} -positioning LN
CXCL14	BRAK	?	Macrophage skin homing (human)
Cxcl15	Lungkine (mouse only)	?	?
CXCL16		CXCR6	NKT and ILC migration and survival
CXCL17		?	Macrophage and DC chemotaxis
CCL1	I-309, mouse TCA3	CCR8	Th2 cell and Treg trafficking
CCL2	MCP-1, mouse JE	CCR2	Inflammatory monocyte trafficking
CCL3	MIP-1 α	CCR1, CCR5	Macrophage and NK-cell migration; T-cell–DC interactions
CCL4	MIP-1 β	CCR5	Macrophage and NK-cell migration; T-cell–DC interactions
CCL5	RANTES	CCR1, CCR3, CCR5	Macrophage and NK-cell migration; T-cell–DC interactions
Ccl6	C-10, MRP-1 (mouse only)	Unknown	?
CCL7	MCP-3, mouse Fic or MARC	CCR2, CCR3	Monocyte mobilization
CCL8	MCP-2	CCR1, CCR2, CCR3, CCR5 (human); CCR8 (mouse)	Th2 response, skin homing mouse
Ccl9/10	MIP-1 γ , MRP-2 (mouse only)	Unknown	?
CCL11	Eotaxin-1	CCR3	Eosinophil and basophil migration
Ccl12	MCP-5 (mouse only)	CCR2	Inflammatory monocyte trafficking
CCL13	MCP-4	CCR2, CCR3, CCR5	Th2 responses
CCL14	HCC-1	CCR1	?
CCL15	Leukotactin-1, HCC-2, MIP-5	CCR1, CCR3	?
CCL16	HCC-4, NCC-4, LEC	CCR1, CCR2, CCR5	?
CCL17	TARC	CCR4	Th2 responses, Th2-cell migration, Treg, lung, and skin homing
CCL18	PARC, DC-CK1	CCR8	Th2 response, marker AAM, skin homing
CCL19	ELC, MIP-3 β	CCR7	T-cell and DC homing to LN
CCL20	MIP-3 α , LARC	CCR6	Th17 responses, B-cell, and DC homing to gut-associated lymphoid tissue
CCL21	SLC, 6CKine	CCR6, CCR7	T-cell and DC homing to LN
CCL22	MDC	CCR4	Th2 response, Th2-cell migration, Treg migration
CCL23	MPIF-1, MIP-3	Unknown	?
CCL24	Eotaxin-2, MPIF-2	CCR3	Eosinophil and basophil migration
CCL25	TECK	CCR9	T-cell homing to gut, thymocyte migration

Continued

Table 1. *Continued*

Chemokine	Other names	Receptor	Key/main immune function
CCL26	Eotaxin-3	CCR3, CX3CR1	Eosinophil and basophil migration
CCL27	CTAK	CCR10	T-cell homing to skin
CCL28	MEC	CCR3, CCR10	T-cell and IgA plasma-cell homing to mucosa
XCL1	Lymphotactin, SCM-1 α	XCR1	Cross presentation by CD8 ⁺ DCs
XCL2	SCM-1 β	XCR1	Cross presentation by CD8 ⁺ DCs
CX3CL1	Fractalkine	CX3CR1	NK, monocyte, and T-cell migration

This table was created from data adapted from Bachelierie et al. 2013.

AAM, alternatively activated macrophage; ILC, innate lymphoid cell; LN, lymph node; NK, natural killer; NKT, natural killer T; T_{FH}, follicular helper T cell; Treg, regulatory T cell.

adjoining amino-terminal cysteine residues, whereas CX3CL1 has three amino acids separating the two initial cysteine residues. Most chemokines are secreted into the extracellular space where they remain soluble or are bound to extracellular matrix components, thus forming transient or stable concentration gradients, respectively. Chemokines and their gradients are detected by binding to specific chemokine receptors.

Chemokine receptors are a group of ~20 rhodopsin-like seven-transmembrane-spanning receptors in humans and mice (Table 2). These receptors are G-protein-coupled and signal via pertussis toxin-sensitive Gi-type G proteins. The chemokine receptors show varying levels of binding specificity and promiscuity. For example, CXCR4 binds only CXCL12, whereas CCR1 can bind to six different chemokine ligands. Despite this promiscuity, chemokine receptors do not bind different groups of chemokines (e.g., CCL and CXCL chemokines), and they are named based on the group that they bind; CCR chemokine receptors bind CCL chemokines, whereas CXCR receptors bind CXCL chemokines. In addition to the signaling receptors, chemokine receptors also include a group of four atypical receptors. These are similar in structure to the signaling receptors, but lack an intracellular motif required for signaling through Gi-type G proteins. These nonsignaling, atypical receptors appear to play primary roles in shaping chemokine gradients by scavenging and promoting transcytosis of chemokine ligands.

EVOLUTION OF CHEMOKINES AND CHEMOKINE RECEPTORS

Chemokines are evolutionarily ancient, having first appeared 700 million years ago in a common ancestor of the vertebrate lineage. Although chemotaxis has been described in invertebrate cells, an analog of the chemokine system does not appear to exist in the invertebrates (DeVries et al. 2006). After their initial appearance, chemokines have undergone extensive and rapid evolution, owing to large gene duplication events and subsequent selection. Human chemokine ligand genes are predominantly found on chromosomes 4 and 17 in regions with significant numbers of pseudogenes, which correlates with a distant gene duplication event with subsequent diversification, selection, and loss (Zlotnik et al. 2006; Nomiya et al. 2010). However, there is significant variation in chemokine ligands between different evolutionary lineages. The zebrafish genome contains more than 100 discrete chemokine genes (Zlotnik et al. 2006; Nomiya et al. 2010). Whether this is the result of selection events attributable to different pathogen exposure or the result of random genetic duplication events remains to be determined.

Similar to chemokine ligands, chemokine receptors show evidence of rapid expansion and evolution after their appearance in a common vertebrate ancestor. The sea lamprey, a jawless fish, contains six known chemokine receptors. Concurrent with their ligands, further expansion of chemokine receptors occurred



Table 2. Chemokine receptors

Receptor	Immune cell expression	Key immune function
G-protein-coupled chemokine receptors		
CXCR1	N>Mo, NK, MC, Ba, CD8 T _{EFF}	Neutrophil trafficking
CXCR2	N>Mo, NK, MC, Ba, CD8 T	B-cell lymphopoiesis Neutrophil egress from bone marrow Neutrophil trafficking
CXCR3	Th1, CD8 T _{CM} and T _{EM} , NK, NKT, pDC, B, Treg, T _{FH}	Th1-type adaptive immunity
CXCR4	Most (if not all) leukocytes	Hematopoiesis Organogenesis Bone marrow homing
CXCR5	B, T _{FH} , T _{FR} , CD8 T _{EM}	B- and T-cell trafficking in lymphoid tissue to B-cell zone/follicles
CXCR6	Th1, Th17, $\gamma\delta$ T, iLC, NKT, NK, PC	Innate lymphoid cell function
CCR1	Mo, M Φ , N, Th1, Ba, DC	Adaptive immunity Innate immunity
CCR2	Mo, M Φ , Th1, iDC, Ba, NK	Adaptive immunity Monocyte trafficking
CCR3	Eo>Ba, MC	Th1-type adaptive immunity Th2-type adaptive immunity
CCR4	Th2, skin- and lung-homing T, Treg>Th17, CD8 T, Mo, B, iDC	Eosinophil distribution and trafficking Homing of T cells to skin and lung Th2-type immune response
CCR5	Mo, M Φ , Th1, NK, Treg, CD8 T, DC, N	Type-1 adaptive immunity
CCR6	Th17>iDC, $\gamma\delta$ T, NKT, NK, Treg, T _{FH}	iDC trafficking, GALT development
CCR7	T _N , T _{CM} , T _{RCM} , mDC, B	Th17 adaptive immune responses mDC, and B- and T-cell trafficking in lymphoid tissue to T-cell zone
CCR8	Th2, Treg, skin T _{RM} , $\gamma\delta$ T, Mo, M Φ	Egress of DC and T cells from tissue Immune surveillance in skin type-2 adaptive immunity, thymopoiesis
CCR9	Gut homing T, thymocytes, B, DC, pDC	Homing of T cells to gut GALT development and function, thymopoiesis
CCR10	Skin-homing T, IgA plasmablasts	Humoral immunity at mucosal sites Immune surveillance in skin
XCR1	Cross-presenting CD8 ⁺ DC, thymic DC	Ag cross-presentation by CD8 ⁺ DCs
CX3CR1	Resident Mo, M Φ , MG, Th1, CD8 T _{EM} , NK, $\gamma\delta$ T, DC	Patrolling monocytes in innate immunity Microglial-cell and NK-cell migration type-1 adaptive immunity
Atypical chemokine receptors (non-G-protein-coupled signaling)		
ACKR1 (DARC; Duffy)	RBC, LEC	Chemokine transcytosis Chemokine scavenging
ACKR2 (D6)	LEC, DC, B	Chemokine scavenging
ACKR3 (CXCR7)	Stromal cells, B	Shaping chemokine gradients for CXCR4
ACKR4 (CCRL1; CCX-CKR)	Thymic epithelium	Chemokine scavenging

Data in table is modified from Bachelierie et al. 2013.

B, B cell; Ba, basophil; Eo, eosinophils; GALT, gut-associated lymphoid tissue; iDC, immature DC; LEC, lymphatic endothelium; M Φ , macrophage; MG, microglia; Mo, monocyte; N, neutrophil; pDC, plasmacytoid DC; PC, plasma cell; RBC, red blood cell; T_{CM}, central memory T cell; T_{EFF}, effector T cell; T_{FH}, follicular helper T cell; T_{FR}, follicular regulatory T cell; T_N, naïve T cell; T_{RCM}, recirculating memory T cell.

with species diversification. The elephant shark, a cartilaginous fish, contains 13 putative chemokine receptors, whereas the zebrafish contains at least 32 different chemokine receptors (Zlotnik et al. 2006). Mammals contain less, indicating that this expansion in chemokine receptors occurred following the split of the teleost lineage with the mammalian lineage. Humans and mice contain 17 signaling chemokine receptors, with the majority present on human chromosome 3 (Zlotnik et al. 2006).

THE CHEMOKINE SYSTEM IN INNATE IMMUNE CELL HOMEOSTASIS

Developing Immune Cells

Maintenance of hematopoietic stem cells and developing innate immune cells takes place largely in the bone marrow (BM) and is dependent on CXCL12/CXCR4 interactions. The retention of hematopoietic stem cells within BM niches is dependent on CXCL12, which is produced by CXCL12-abundant reticular cells, and binds to CXCR4 on hematopoietic stem cells (Ara et al. 2003). As immune cell development progresses past the hematopoietic stem cell, CXCL12/CXCR4 interactions remain essential for BM retention and normal development of multiple immune lineages, including B cells, monocytes, macrophages, neutrophils, natural killer (NK) cells, and plasmacytoid dendritic cells (Mercier et al. 2012). Developing neutrophils are retained in the BM by CXCR4 signals, and their maturation coincides with down-regulation of CXCR4, permitting mature neutrophils to enter the peripheral blood (Suratt et al. 2004; Broxmeyer et al. 2005). This process is defective in patients with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, which is caused by mutations in CXCR4 that enhance responsiveness to CXCL12 (Hernandez et al. 2003; Gulino et al. 2004). Neutrophils in the WHIM syndrome are unable to normally decrease responsiveness to CXCL12 and are therefore trapped within the BM, resulting in peripheral neutropenia.

CXCR4-mediated signaling plays a major role in promoting BM retention of many im-

mune cells. However, exit from the BM may not be entirely passive. In studies examining monocyte development and release from the BM, blockade of CXCR4 induces only a small increase in the number of peripheral blood monocytes (Wang et al. 2009). However, blockade of CCR2, which is uniformly expressed by early monocytes, leads to decreases in circulating monocytes with concomitant increases in BM monocytes (Serbina and Pamer 2006; Wang et al. 2009). However, the source of CCR2 ligands under homeostatic conditions is unclear.

Neutrophils

After release from the BM, neutrophils enter the bloodstream where they await inflammatory stimuli that would promote their migration into peripheral tissue. The peripheral bloodstream is thought to be the major compartment for neutrophils under homeostatic conditions; however, recent reports indicate that CXCR4 signaling may promote the formation of a marginated pool of neutrophils in the lung vasculature that can be rapidly mobilized (Devi et al. 2013). CXCR4 may also play an important role in neutrophil elimination; senescent neutrophils up-regulate expression of CXCR4 and this may promote reentry into the BM where they undergo apoptotic cell death (Martin et al. 2003).

Monocytes

Exit of monocytes from the BM appears to be dependent on CXCR4 and possibly CCR2-mediated signaling under homeostatic conditions. Upon exiting, monocytes differentiate into proinflammatory and anti-inflammatory subsets based on their expression of CCR2 and CX3CR1, respectively. The proinflammatory (CCR2⁺) monocyte population remains within the peripheral blood and spleen, whereas the anti-inflammatory (CX3CR1⁺) population is distributed in the peripheral blood and nonlymphoid organs (Fig. 1) (Geissmann et al. 2003). This is likely because of differential homeostatic expression of CCR2 and CX3CR1 ligands; in the absence of inflammation, there is little expres-

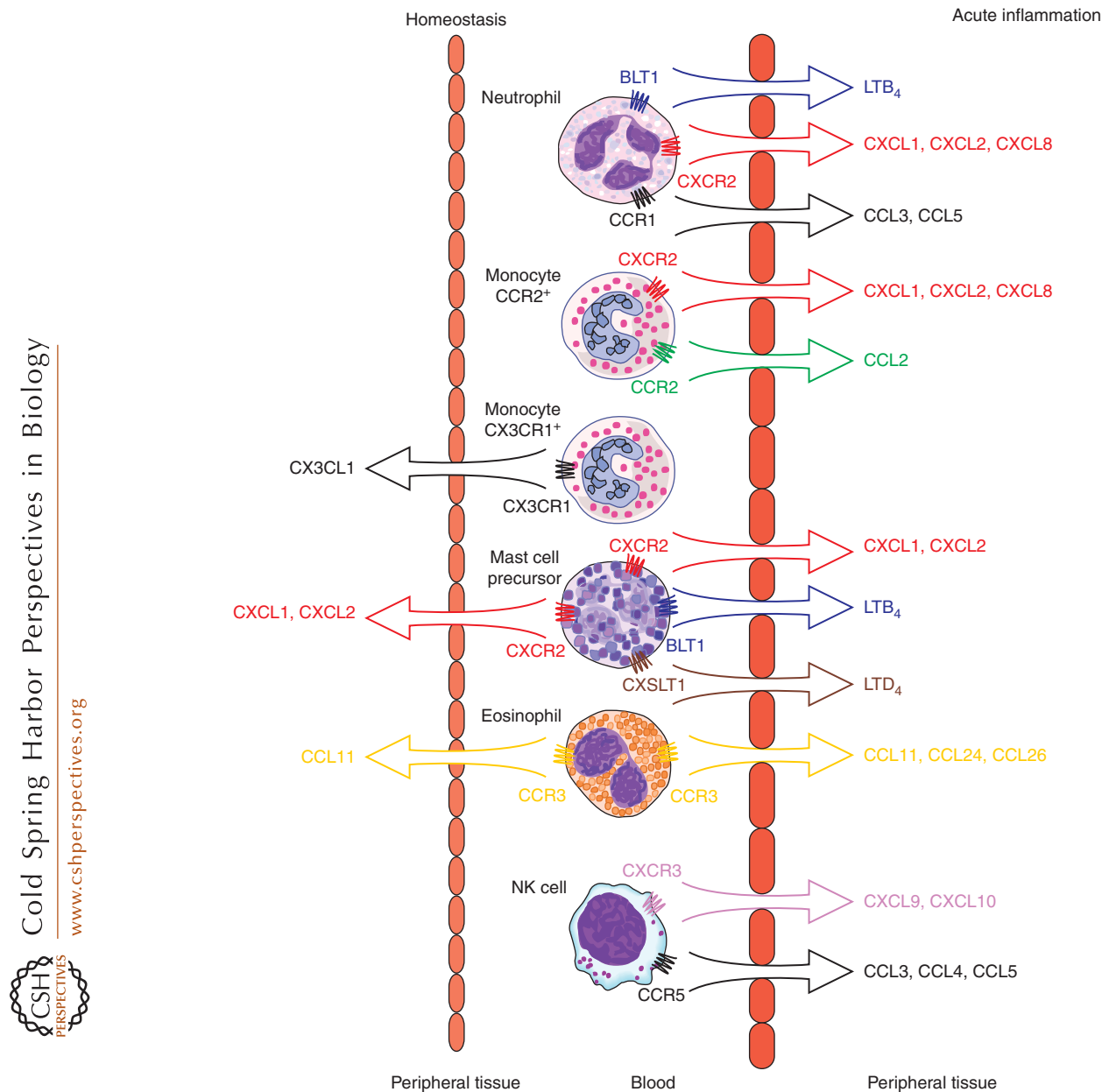


Figure 1. Chemokine control of innate immune cell migration in homeostasis and inflammation. Under homeostatic conditions, CX3CR1⁺ monocytes presumably migrate into the periphery following CX3CL1 gradients, mast cell precursors migrate into the gastrointestinal tract following CXCL1 and CXCL2 gradients, and eosinophils migrate into tissue following CCL11 gradients. In acute inflammation, neutrophils may leave the bloodstream and migrate into the periphery following gradients of LTB₄, CXCL1, CXCL2, CXCL8, CCL3, and CCL5. CCR2⁺ monocytes will migrate following CXCL1, CXCL2, CXCL8, and CCL2 gradients. Mast cell precursors also migrate in response to leukotriene B4 (LTB₄) and leukotriene D4 (LTD₄) via activation of their respective G-protein-coupled receptors BLT1 and CYSLT1. Eosinophils will migrate into inflammatory sites in response to CCL11, CCL24, and CCL26 gradients. NK cells will migrate following CXCL9, CXCL10, CCL3, CCL4, and CCL5 gradients.



sion of CCR2 ligands in the periphery, whereas CX3CL1 is homeostatically expressed by endothelium in various tissues (Foussat et al. 2000). However, CX3CR1⁺ monocytes may follow additional chemokine signals as they enter the periphery and develop into tissue macrophages under homeostatic conditions. CXCL14 is homeostatically produced by human fibroblasts in the skin and lamina propria, and tissue macrophages can be found in close association with CXCL14-producing cells (Kurth et al. 2001). However, the full role of CXCL14 and its receptor, which remains to be identified, is not fully appreciated.

Eosinophils and Basophils

Under homeostatic conditions, eosinophils are found in the blood and the peripheral tissues, with the gastrointestinal tract making up the main reservoir of eosinophils. This baseline migration into the periphery is largely dependent on the production of CCL11 (eotaxin-1)/CCR3 interactions that promote eosinophil release from the BM and entry into peripheral tissues (Fig. 1) (Palframan et al. 1998; Mishra et al. 1999). Basophils express CXCR4 and so it is possible that they are released into the peripheral blood by CXCR4-mediated mechanisms, where they remain in the absence of inflammatory stimuli. Human basophils constitutively express CXCR1, CXCR4, CCR1, CCR2, and a majority express CCR3 (Ugucioni et al. 1997; Marone et al. 2005).

Mast Cells

Mast cells (MCs) are found throughout all vascularized tissues, where they act as innate immune sentinels and effector cells. MC precursors express CXCR4, as well as CXCR2, CCR3, and CCR5, and likely exit the BM following similar pathways to other innate immune cells (Ochi et al. 1999). They then migrate into the periphery via unknown mechanisms, although migration in response to epithelial- and fibroblast-derived stem cell factor (SCF) has been postulated (Nilsson et al. 1996). Migration signals may be tissue dependent; CXCR2 deficiency in MC precursors leads to a specific de-

fect in intestinal homing of MC precursors and loss of intestinal MCs (Fig. 1) (Abonia et al. 2005). Once in the peripheral tissues, MCs further differentiate and alter their chemokine receptor expression; whether this is because of constitutive signaling necessary for tissue retention is unknown (Halova et al. 2012).

Dendritic Cells

Under homeostatic conditions, dendritic cells (DCs) develop in situ from DC precursor cells that first populate the periphery. No common chemokine for DC precursor positioning has been described and the chemokines that guide this transit remain largely unknown, although CCL2, CXCL14, and CCL20 have been implicated. CCR2 deficiency leads to decreases in the skin resident langerin-positive DCs, but not in other DC populations (Bogunovic et al. 2006). CCL20/CCR6 interactions are essential for normal DC migration to the subepithelial dome of the Peyer's patches, but no other DC populations are affected (Cook et al. 2000; Varona et al. 2001). Finally, CXCL14 has been postulated to play a role in DC precursor positioning based on its ability to induce chemotaxis in human DC precursors (Schaerli et al. 2005). However, CXCL14-deficient mice show no defect in DC positioning, casting doubt on the universal role of CXCL14 in DC positioning (Meuter et al. 2007).

DC precursors differentiate into immature resident DCs that survey the periphery for signs of infection or inflammation. Immature, resident DCs express various chemokine receptors (e.g., CCR1, CCR2, CCR5, CCR6, CXCR1, CXCR2, and CXCR4) that allow DCs to migrate to sites of inflammation, but they may also actively promote their maintenance in the periphery (Randolph et al. 2008). However, even in the absence of inflammatory stimuli, DCs can become "semi-mature," a state defined by increased surface expression of major histocompatibility complex class II (MHCII) and CCR7. The up-regulation of CCR7 allows these DCs to sense CCL21, which is produced by the lymphatic vessels in peripheral tissues, thus permitting semi-mature DCs to migrate into the lym-

phatics (Forster et al. 1999; Weber et al. 2013). CCR7 signaling is a common pathway for homeostatic DC migration from diverse peripheral tissues; CCR7 has been shown to be essential for migration of DCs from the skin, lung, and gastrointestinal tract (Ohl et al. 2004; Worbs et al. 2006). However, there is redundancy in CCR7 ligands; within the peripheral tissues, CCL21 promotes migration to the lymphatic vessels, but once inside the vessel, CCL19 and CCL21 act additively to promote migration to the lymph node (LN).

Because soluble or particulate antigens may have direct access to the secondary lymphoid organs via the lymphatics or bloodstream, proper homeostatic positioning of DCs within the secondary lymphoid organs is essential for immune defense. Within the LN, the fibroblastic reticular cells homeostatically produce CCL19 and CCL21, which promote DC localization to the T-cell area. In the spleen, CD4⁺ DCs express high levels of the G-protein-coupled receptor EBI2, the receptor for 7 α , 25-dihydroxycholesterol, which is necessary for the normal positioning of CD4⁺ DCs in the bridging channels of the spleen and the subsequent immune response to particulate antigens (Gatto et al. 2013). Finally, although sphingosine-1-phosphate receptor 1 (S1PR1) blockade has no effect on DC localization in the LN, it does lead to the redistribution of immature CD4⁺ DCs from the bridging channels to the splenic marginal zone (Czeloth et al. 2007). This is specific to DC localization under homeostatic conditions; activated or mature DC positioning is not affected. Thus, although DC migration is a universal pathway governed by CCR7 signaling, positioning in the periphery and secondary lymphoid organs may be specific for different DC subsets.

Innate Lymphoid Cells

Innate lymphoid cells (ILCs) are a broad group of innate lymphocyte-like cells that are notable for not undergoing recombination of antigen receptors and clonal selection. They have been organized into three groups based on cytokine production. Group 1 ILCs includes ILC1 and classical NK cells. Human NK cells can be split

into CD56^{dim} and CD56^{bright} populations. Under homeostatic conditions, CD56^{dim} NK cells comprise the majority of blood resident NK cells, whereas CD56^{bright} are preferentially localized to secondary lymphoid organs. As expected, this differential localization is accompanied by differences in chemokine receptor expression. Although all NK cells express CXCR1, CXCR3, and CXCR4, CD56^{high} NK cells also express CCR7, allowing for homeostatic migration to the LNs (Maghazachi 2010). Group 2 ILCs include ILC2, also referred to as natural helper cells or nuocytes. ILC2 express CXCR4 and CCR9, which promote their homeostatic distribution (Walker et al. 2013). Using a CXCR6 reporter mouse, ~50% of ILC2 was also shown to express the CXCR6 reporter (Roediger et al. 2013). However, ILC2 may not actually express CXCR6 and expression of the reporter may simply reflect prior expression by an ILC2 precursor cell (Possot et al. 2011; Constantinides et al. 2014). Finally, group 3 ILCs include ILC3 and lymphoid tissue-inducer (LTi) cells. LTi cells differentiate from a CXCR6^{high} LTi precursor cell and the mature LTi cells express CXCR5 and CCR6 (Constantinides et al. 2014). This CCR6 expression allows LTi cells to migrate into the intestinal epithelium in response to epithelial derived CCL20 and β -defensins, which are produced in response to commensal bacteria (Sawa et al. 2010).

THE CHEMOKINE SYSTEM IN ACUTE INFLAMMATION

Acute inflammation is a complex process that must coordinate the dual goals of providing initial immune protection as well as to initiate the adaptive immune response. This coordination starts with the homeostatic prepositioning of innate immune cells throughout the periphery, where they act as local sensors of infection and inflammation through the activation of pattern recognition receptors (PRRs), the inflammasome, and/or RNA and DNA sensors. Examples of these prepositioned cellular sensors of infection or inflammation include MCs, macrophages, and DCs. Upon activation, these local innate immune cells release inflammatory cyto-



kines and chemokines that promote the entry of additional, often blood resident, innate effector cells such as neutrophils and monocytes. These cells follow chemokine gradients to the site of inflammation, but can themselves be activated to produce additional inflammatory cytokines and chemokines that promote further inflammatory cell entry. This feed-forward mechanism not only allows for rapid amplification of the effector response, but also allows the innate immune system to shape the inflammatory response. At the same time, activated DCs change their responsiveness to chemokine gradients, allowing for rapid migration to secondary lymphoid organs and initiation of the adaptive immune response. We will discuss the role of the chemokine system in shaping the acute inflammatory response as well as its role in shaping the activation of the adaptive immune response.

Induction of Acute Inflammation by Resident Immune Cells

With the exception of neutrophils, monocytes, and basophils, almost all innate immune cells are present to some extent in the periphery under homeostatic conditions. There they lie in wait as sensors of pathogen invasion, via PRRs, or tissue damage, via the interleukin (IL)-33 pathway as one example. MCs and macrophages are classically described as essential immune sensors, based on their expression of a wide variety of PRRs and their broad localization throughout all vascularized tissues. MCs are uniquely capable of responding immediately to infectious or inflammatory stimuli. Lipopolysaccharide (LPS) stimulation of murine peritoneal MCs leads to immediate release of CXCL1 and CXCL2-containing granules, but not histamine-containing granules, as well as transcriptional activation of CXCL1 and CXCL2. This promotes early (within 2 h of stimulus) neutrophil recruitment that is abolished in MC-depleted mice, but not in macrophage-depleted mice (De Filippo et al. 2013). Additionally, in mouse models of airway hyperreactivity, MCs release preformed CCL1, promoting early migration of CCR8 expressing Th2 effector cells (Gonzalo et al. 2007). However, release of pre-

formed mediators acts only temporarily to promote inflammatory cell entry; sustained recruitment requires transcriptional activation and secretion of additional chemokines.

Although preformed MC chemokines are necessary for immediate neutrophil recruitment in an LPS intraperitoneal injection model, neutrophil migration is normal in MC-deficient mice within 4 h after LPS injection (De Filippo et al. 2013). This is attributable to chemokine production by macrophages, which produce a wide range of chemokines including, but not limited to, CXCL1, CXCL2, CXCL8, CCL2, CCL3, CCL4, and CCL5. Similarly, MCs have been shown to produce CCL2, CCL3, CCL4, CCL5, CCL11, CCL20, CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, and CXCL11 (Marshall 2004). Finally, viral exposure of DCs leads to the production of many of the same chemokines as well as CXCL16 (Piqueras et al. 2006). Group 2 ILCs appear to play an important role in acute inflammation in response to epithelial damage. IL-33 produced in response to epithelial damage by the protease allergen papain activates ILC2, leading to their production of CCL17 and CCL22 (Halim et al. 2014). Depletion of any of these cell types results in impaired inflammatory cell migration, although the degree of impairment is dependent on the model used.

In addition to producing chemokines, resident innate immune cells also produce inflammatory cytokines, such as tumor necrosis factor (TNF) and IL-1. These cytokines can alter the chemokine environment by inducing further production of chemokines, altering the presentation of chemokines by endothelium, or by altering the response to chemokine gradients. Cytokine-activated epithelium can produce a host of chemokines, including CCL2, CCL3, CCL4, CCL5, CXCL1, CXCL2, CXCL3, CXCL5, and CXCL8 (Kagnoff and Eckmann 1997). Likewise, cytokines can alter chemokine presentation by endothelial cells. In a model of experimental autoimmune encephalitis, IL-17 stimulation of brain endothelial cells leads to abluminal expression of CXCR7, which acts to remove CXCL12. In the absence of endothelial CXCL12, leukocytes enter the brain and induce disease pathogenesis (Cruz-Orengo et al. 2011).

Whether this occurs in other disease settings and in other organs remains to be seen. Finally, cytokines can also impact the responsiveness of immune cells to available chemokines. For instance, activated ILC2 releases IL-13, which promotes increased DC responsiveness to CCR7 ligands and thus induces DC migration into the draining LNs (Halim et al. 2014).

ENTRY OF BLOOD-BORNE CELLS INTO SITES OF ACUTE INFLAMMATION

Neutrophils

Although resident innate immune cells are the initial responders to inflammatory cues, circulating innate cells such as neutrophils, monocytes, and eosinophils quickly become the major immune cells during acute inflammation. Neutrophils are stereotypical cells of acute inflammation; they express many chemokine receptors, including CXCR2 and CCR1 in mice and CXCR1 and CXCR2 in humans, which respond to early chemokines released by MCs and macrophages (Fig. 1). Once activated in tissue, neutrophils up-regulate other chemokine receptors, such as CCR5, which has been shown to act as a chemokine scavenger (Ariel et al. 2006). Neutrophils also express chemotactic receptors for complement, lipid mediators, such as leukotriene B₄ (LTB₄), and bacterial products, such as formylated peptides, including formyl-methionyl-leucyl-phenylalanine (fMLP). But how do neutrophils respond to distant chemokine gradients that exist beyond the endothelium? As previously discussed, endothelial cells can be activated by inflammatory cytokines produced by innate immune cells. Additionally, the pericyte, a structural support cell of the endothelium, has been shown to be a “hot spot” for neutrophil migration and to up-regulate adhesion molecules and chemokines after activation via PRRs (Proebstl et al. 2012; Stark et al. 2013). This activation induces the endothelial expression of P-selectin, E-selectin, and integrins, which bind to neutrophils, slowing their movement and causing them to roll along the endothelium. Rolling neutrophils are then able to bind to chemokines, such as CXCL1, CXCL2, or CXCL8, which are presented on the luminal

surface of the endothelium. There are two established sources for these luminal chemokines: direct production by the activated endothelium or endothelial presentation of distantly produced chemokines. In the second case, the atypical chemokine receptor, known as the Duffy antigen receptor for chemokines (DARC or ACKR1), binds free chemokines on the abluminal surface of the endothelium. The DARC/chemokine complex is then transcytosed across the endothelial cell and ultimately presented on the luminal surface, where the bound chemokine is able to activate and promote immune cell transmigration (Proudfoot et al. 2003; Pruenster et al. 2009). Given the indiscriminate tissue damage seen in acute inflammation, this process is under tight control with rapid endocytosis and destruction of immobilized chemokines (Hillyer and Male 2005).

Once they have transcytosed, neutrophils follow chemoattractant gradients as they migrate through the interstitium to sites of acute inflammation. Along the way, activated neutrophils produce CCL3, CCL4, CCL5, CCL20, CXCL1, CXCL8, CXCL9, and CXCL10. Thus, they can further amplify the initial acute inflammatory response by inducing additional leukocyte entry (Bennouna et al. 2003). Chemokines make up one class of chemoattractants; however, neutrophils can respond to a wide variety of chemoattractant molecules that include lipid mediators, bacterial products, and complement fragments. These different classes of chemoattractants can act simultaneously or sequentially. One example of sequential activity of chemoattractants is in a model of sterile thermal tissue injury. In this model, CXCL2 gradients form around the area of tissue injury and promote neutrophil chemotaxis toward the injury site (McDonald et al. 2010). However, because chemokine production is dependent on live cells, the central site of necrosis lacked a supportive CXCL2 gradient. Instead, endogenous formyl peptides, which are produced by mitochondria and released upon cellular damage, promoted neutrophil chemotaxis to the site of cellular injury (McDonald et al. 2010; Zhang et al. 2010). Thus, CXCL2 gradients promoted initial migration to the area of necrosis, followed by FPR1

signaling that promoted neutrophil entry into the necrotic center (Fig. 2A).

Beyond providing linear directional information, different chemoattractant classes may play important roles in permitting neutrophils to amplify their own migration. Such interactions between chemoattractant classes have been shown in the case of LTB_4 and chemokines. Using a mouse model of autoimmune arthritis,

we and other investigators have shown that LTB_4 acting through the G-protein-coupled receptor BLT1 on neutrophils is necessary for initial neutrophil recruitment into the joint (Chen et al. 2006; Kim et al. 2006). Once inside the joint, these initial “scout” neutrophils are activated by synovial-immune complexes to produce neutrophil-active chemokines, such as CXCL2, as well as the proinflammatory cytokine IL-1 β .

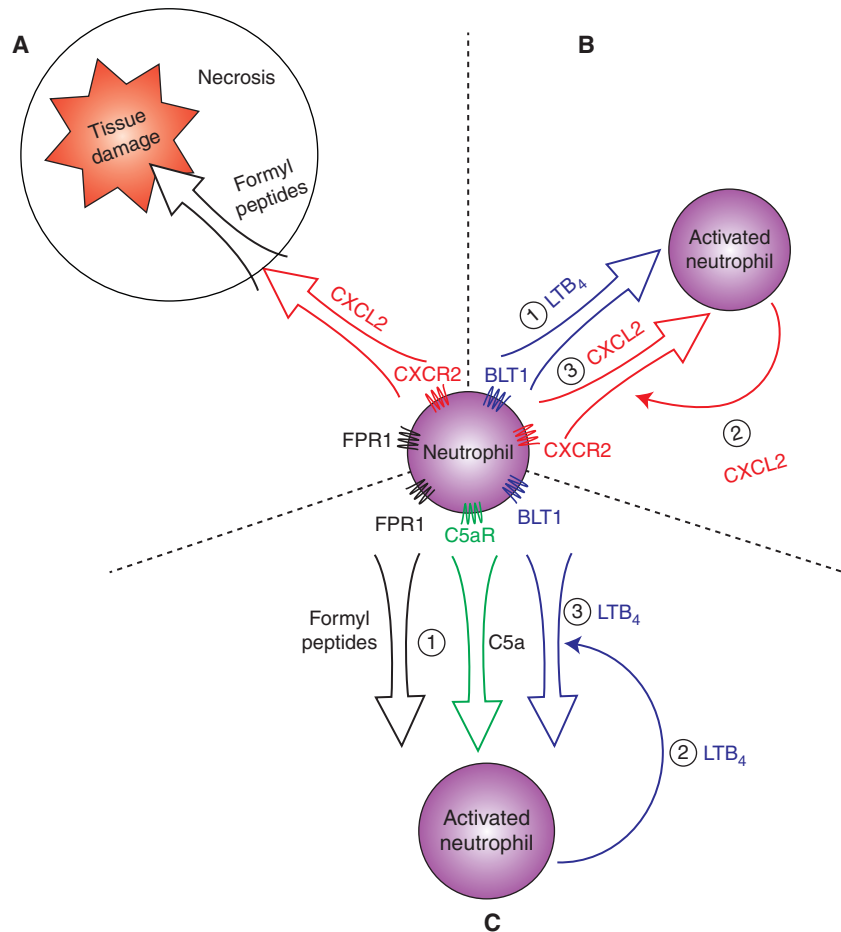


Figure 2. Mechanisms of neutrophil migration in the inflamed periphery. (A) Neutrophils migrate to sites of tissue damage by following sequential chemoattractant gradients. Neutrophils first follow CXCL2 gradients, and then, in areas of tissue necrosis, follow gradients of endogenous formyl peptides via FPR1 signaling. (B) Neutrophils can amplify their own recruitment through the production of chemokines. Neutrophils migrate to inflammatory sites by following LTB_4 gradients (1) where they are activated by inflammatory stimuli and produce additional chemokines, such as CXCL2 (2) that promote further neutrophil entry by establishing an additional chemokine gradient (3). (C) Neutrophils can be activated by chemotactic agents, such as formyl peptides or C5a, leading to LTB_4 production, which establishes a relay system for neutrophil swarming. Formyl-peptide or C5a-activated neutrophils (1) produce LTB_4 (2), which creates a chemoattractant gradient that induces more neutrophils to enter and swarm to the site of inflammation (3).

This inflammatory cytokine then activates local synoviocytes as well as macrophages and endothelial cells to produce additional acute inflammatory chemokines, such as CCL3, CCL4, CCL5, CXCL1, and CXCL2. These chemokines then rapidly amplify neutrophil entry into the joint by binding to the CCR1 and CXCR2 receptors on neutrophils (Chou et al. 2010). Thus, LTB_4 induces a necessary initial neutrophil migration that then amplifies inflammatory cell influx characteristic of acute inflammation (Fig. 2B).

In addition to creating sequential waves of neutrophil recruitment, different chemoattractant classes may enhance the response to each other or act to amplify the chemotactic gradient. Stimulation of the G-protein-coupled formyl peptide receptor FPR1 on neutrophils leads to neutrophil LTB_4 production, which then feeds back in an autocrine and paracrine fashion and promotes further neutrophil migration toward formyl peptides (Afonso et al. 2012). Likewise, in the murine model of immune-complex-induced arthritis discussed above, activation of the G-protein-coupled complement receptor C5aR was required for the generation of LTB_4 and the induction of arthritis (Sadik et al. 2012). Indeed, production of LTB_4 by neutrophils appears to be an essential mechanism for extending the range and enhancing the stability of chemotactic signals. Activated neutrophils produce LTB_4 , which then acts as a neutrophil chemoattractant. Thus, LTB_4 production by activated neutrophils can feed-forward and extend the range of initial chemotactic signals. Additionally, this LTB_4 can activate neutrophils, promoting further LTB_4 production, which acts to further amplify the initial inflammatory stimulus (Afonso et al. 2012). LTB_4 -mediated amplification of neutrophil activation and chemotaxis induces the coordinated chemotaxis and clustering (i.e., swarming) of neutrophils at sites of tissue damage in vivo (Fig. 2C) (Lammermann et al. 2013).

Monocytes

Along with neutrophils, blood-borne monocytes are recruited early in the setting of acute

inflammation by activated endothelium. As discussed previously, monocytes are divided into $CCR2^+$ and $CX3CR1^+$ groups. $CCR2^+$ monocytes are largely resident in the peripheral blood during homeostasis, but rapidly migrate to areas of acute inflammation. Although they are defined by their expression of CCR2, they also express CXCR2, which may play an important role in initial activation and transmigration. In an atheroma model, CXCL8/CXCR2 interactions were necessary for firm adhesion of monocytes to vascular endothelium (Gerszten et al. 1999). CCR2 signaling then promotes proinflammatory monocyte migration into peripheral tissues in response to stable extracellular matrix-associated CCL2 gradients (Fig. 1) (Kuziel et al. 1997; Proudfoot et al. 2003). Interestingly, although CXCL2 does not appear to promote monocyte migration in response to CXCL8, it does promote migration in response to its atypical ligand macrophage migration inhibitory factor (MIF). MIF binds to CD74 and CXCR2 on monocytes and macrophages, leading to CXCR2 signaling and integrin-dependent chemotaxis of monocytes, which is necessary for maintenance of atherosclerotic plaques (Bernhagen et al. 2007). Additionally, CCR1 and CCR5 have been shown to promote chemotaxis of $CCR2^+$ monocytes in in vitro experiments, but in vivo data are lacking (Weber et al. 2001; Le Borgne et al. 2006; Shi and Pamer 2011).

In addition to promoting $CCR2^+$ monocyte recruitment to sites of acute inflammation, CCL2 may also have long-range effects in draining LNs and BM. Soluble CCL2 has been detected in the afferent lymph, where it drains to the LN, binds to HEVs, and induces $CCR2^+$ monocyte entry into the draining LN (Palframan et al. 2001). Additionally, CCL2 plays an important role in mobilizing inflammatory monocytes from the BM (Fig. 1). The source of this CCL2 is unclear. It is possible that locally produced CCL2 enters the systemic circulation, but given the mechanisms in place to remove circulating chemokines, there may not be sufficient concentrations of CCL2 that reach the BM. Alternatively, small amounts of pathogen-associated molecular patterns may enter the systemic cir-

ulation during infection, activate PRRs on BM niche cells, and induce local CCL2 production by BM cells (Shi et al. 2011). Given the heterogeneity of acute inflammatory stimuli that induce monocyte egress, it is likely that multiple mechanisms contribute to the chemokine-dependent mobilization of inflammatory monocytes.

The chemotactic properties of CX3CR1⁺ monocytes are less understood. Anti-inflammatory monocytes are characterized by their high-level expression of CX3CR1 and lack of CCR2, although CCR2⁺ monocytes also express intermediate levels of CX3CR1, and CX3CR1 deficiency leads to minimal defects in migration of monocytes. CX3CR1 was shown to play a role in the early migration of inflammatory monocytes into the spleen after *Listeria* infection, but this was a temporary defect (Auffray et al. 2007). Instead, CX3CR1 may fulfill nonchemotactic roles. CX3CR1 has been shown to play an essential role in promoting integrin-mediated adhesion within the vessel, which allows for the patrolling phenotype of CX3CR1⁺ monocytes (Auffray et al. 2007). Additionally, CX3CR1 may provide a prosurvival signal to CX3CR1⁺ monocytes, which may underlie the proatherogenic role of CX3CL1/CX3CR1 (Moatti et al. 2001; Landsman et al. 2009).

Eosinophils

Eosinophils express the chemokine receptors CCR1 and CCR3, allowing them to respond to a wide variety of inflammatory stimuli. However, eosinophils are best characterized by their role in allergic and parasitic responses, during which they migrate in response to the eotaxins (CCL11, CCL24, and CCL26). Eotaxins can be released directly by stimulation of innate immune cells, but experiments in murine asthma models have illustrated that IL-4 and IL-13 exposure are necessary for optimal production of CCL11, CCL24, and CCL26 (Menzies-Gow and Robinson 2001). In murine models of airway inflammation, CCL11 and CCL24 play additive roles in promoting eosinophil migration into the lung (Humbles et al. 2002; Mattes et al.

2002; Pope et al. 2005). The role of CCL26 is less understood, but it likely plays an important role in human eosinophil migration as it is the predominant chemokine that drives eosinophil migration across IL-4-activated endothelial and epithelial monolayers (Fig. 1) (Cuvelier and Patel 2001; Yuan et al. 2006). CCL11 activity is regulated by CD26, a cell-surface protease that cleaves CCL11 into a partial antagonist: a protein that cannot induce chemotaxis, but can still bind to CCR3 and desensitize its response to CCL11. This leads to the inhibition of CCR3-mediated chemotaxis, and ultimately to the suppression of eosinophilic inflammation (Struyf et al. 1999; Yan et al. 2012). Finally, analogous to the inflammation-amplification mechanisms used by other acute inflammatory cells, thymic stromal lymphopoietin (TSLP)-stimulated eosinophils also produce CCL2, CXCL1, and CXCL8 promoting further influx of inflammatory monocytes and neutrophils (Wong et al. 2010).

Dendritic Cells

Once activated by inflammatory cytokines or PRR ligation, DCs undergo a maturation process and down-regulate expression of chemokine receptors expressed on immature DCs and up-regulate CCR7 expression (Sallusto et al. 1998). Thus, instead of altering the expression of chemokine ligands, DC migration occurs in response to alterations in chemokine receptor expression. Mature, CCR7^{high}, DCs follow stable gradients of CCL21, which increase the mobility and directional migration of mature DCs toward the lymphatic endothelium (Tal et al. 2011). There, DCs enter the lumen of the lymphatic vessel via gaps in the basement membrane beneath the lymphatic endothelial cells (Pflücke and Sixt 2009). Once in the lumen, they crawl along following the direction of lymphatic flow until they reach the collecting lymphatics, at which point they freely flow with the lymph to the draining LN and then transmigrate through the floor of the subcapsular sinus and into the T-cell zone in a CCR7-dependent process (Braun et al. 2011).

Innate Lymphoid Cells

As discussed above, innate lymphocytes are thought to primarily be tissue resident in order to provide a first line of defense, especially at mucosal sites. However, parabiosis studies have revealed that there are both tissue-resident and recirculating populations of NK and natural killer T (NKT) cells (Thomas et al. 2011; Sojka et al. 2014). Innate lymphocytes constitutively express inflammatory chemokine receptors, which allow them to rapidly migrate and respond to inflammatory stimuli. NK cells use CCR5 signaling to migrate to sites of acute inflammation in murine-infection models, whereas CXCR3 signaling is used in models of cardiac transplant and hepatitis (Hancock et al. 2001; Hokeness et al. 2005; Khan et al. 2006; Wald et al. 2006). The infiltration of activated, IFN- γ -producing NK cells into peripheral tissues then promotes further cell migration via production of the IFN- γ -inducible CXCR3 ligands, CXCL9 and CXCL10 (Fig. 1). NKT cells have similarly been shown to initially migrate into the acutely inflamed liver via a CXCR6-dependent process where they then promote local accumulation of monocytes and macrophages (Wehr et al. 2013). Chemokine-mediated trafficking of innate lymphoid cells also serves to link innate and adaptive immune responses. For example, CXCR3-mediated NK cell migration guides IFN- γ -secreting NK cells into the LN where they help prime the LN for a Th1 response (Martin-Fontecha et al. 2004). Similarly, in the periphery, a blockade of NK cell CX3CR1-mediated migration into the brain in a mouse model of experimental autoimmune encephalitis led to enhanced disease caused by unabated Th17 formation in the absence of NK-cell-derived IFN- γ (Hao et al. 2010).

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Once in the draining LN or other secondary lymphoid organ, mature DCs migrate to specific regions and secrete their own chemokines to enhance their interactions with adaptive immune cells. The combination of specific lo-

calization and chemoattraction of adaptive immune cells appears to be necessary for optimal activation and instruction of the developing adaptive immune response.

CD4⁺ Th1 Priming

Th1 cells have been shown to preferentially express the chemokine receptors CCR5, CXCR3, and CXCR6, but CXCR3 may play a specific role in CD4⁺ Th1 priming (Bromley et al. 2008; Groom et al. 2012). In response to cutaneous immunization with antigen-pulsed mature DCs or immunization with antigen and adjuvant, CXCL9 and CXCL10 were produced in the interfollicular and medullary regions, respectively, in the draining LN. This expression promoted migration of CD4⁺ T cells to these DC-rich regions, while, at the same time, activated DCs produced CXCL10. Together, this led to clustering and the formation of stable contacts between CD4⁺ T cells and DCs, which were necessary for optimal Th1 differentiation (Groom et al. 2012). In addition to promoting direct interactions between CD4⁺ T cells and DCs, this localization may also place developing Th1 cells close to innate sources of IFN- γ , such as CXCR3 expressing NK, NKT, $\gamma\delta$ T, and innate-like CD8⁺ T cells (Bajenoff et al. 2006; Groom and Luster 2011; Kastenmuller et al. 2012; Oghumu et al. 2013).

CD4⁺ Th2 and Tfh Priming

Like CD4⁺ Th1 cells, optimal induction of Th2 cell differentiation appears to be dependent on chemokine guidance. Using a helminth infection model, Th2 and T follicular helper (Tfh) cell induction was shown to be dependent on CXCL13/CXCR5 interactions (Leon et al. 2012). CXCR5-mediated signaling in both DCs and CD4⁺ T cells led to migration to the perifollicular regions of the LN in response to B-cell-derived CXCL13. A blockade of CXCR5 signaling prevented optimal Th2 and Tfh differentiation (Leon et al. 2012). However, it remains unclear why localization to this region is necessary for Th2 differentiation and whether an innate immune cell involved in cytokine pro-

duction or Th2 skewing cell is similarly localized to this region.

CD8⁺ T-Cell Priming

Optimal priming of CD8⁺ T cells requires interactions with DCs that have been “licensed” by CD4⁺ T cells. This requires the coordinated migration of DCs, CD4⁺ T cells and CD8⁺ T cells, which appears to be caused by CCR5- and CCR4-mediated signaling. In response to CD4⁺ T-cell and DC interactions, both cells secrete CCR5 ligands, which bind to a subset of CD8⁺ T cells within the LN (Castellino et al. 2006). This promotes sustained contacts between CD8⁺ T cells and the CD4⁺ licensed DCs, which is necessary for optimal CD8⁺ T-cell memory responses. However, the precise role for CCR5 remains unclear as viral infection models using different vaccinia virus strains have shown contradictory results for the role of CCR5 in CD8⁺ T-cell priming (Hickman et al. 2011; Kastenmuller et al. 2013). Finally, in a model of CD8⁺ T-cell priming using injection of α -galactosylceramide, CCR4 signaling promoted stable contacts between CD8⁺ T cells and DCs (Semmling et al. 2010). However, whether this pathway is relevant in the setting of more physiologic immune stimuli remains unknown.

CONCLUDING REMARKS

Chemokines are essential for the positioning of innate immune sentinels at mucosal barriers and for the recruitment of the first line of innate immune effector cells to sites of infection and inflammation. Chemokine function is also essential for maintaining an adequate pool of circulating immune cells at homeostasis and at times of stress by governing their release from the BM. Once in the tissue, chemokines collaborate with other chemoattractants, such as lipid mediators, formylated peptides, and complement components, to guide innate immune effectors to the very site of tissue damage and pathogen replication. Chemokine function is also necessary to translate an innate immune response into an adaptive immune response.

Innate immune stimuli—through activation of PRRs—set in motion a genetic program that induces the expression of chemokines from resident tissue innate immune cells and also modulates the expression of chemokine receptors on DCs. The induction of chemokine and chemokine receptor expression orchestrates the movement of antigen-loaded DCs from the tissue into lymphoid tissue to activate T and B cells to initiate the adaptive immune response. Chemokines downstream from PRR activation also help guide the newly activated T cells back into the tissue where the innate immune system first sensed the foreign challenge. In addition, during secondary immune responses, chemokines induced by antigen-specific lymphocyte responses recruit innate immune cells into sites of inflammation, serving to amplify the adaptive response with innate immune effector cells. Thus, chemokines and their receptors serve a critical function in coordinating the interdependent innate and adaptive immune responses.

ACKNOWLEDGMENTS

The writers are supported by grants from the National Institutes of Health, and C.L.S. is also supported by the Asthma and Allergy Foundation of America. We thank Jason Griffith for helpful discussions in the preparation of this manuscript.

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