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invited review

Chemokines and chemokine receptors in leukocyte trafficking

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Olson, Timothy S., and Klaus Ley. Chemokines and chemokine receptors in leukocyte trafficking. *Am J Physiol Regulatory Integrative Comp Physiol* 283: R7–R28, 2002; 10.1152/ajpregu.00738.2001.— Chemokines regulate inflammation, leukocyte trafficking, and immune cell differentiation. The role of chemokines in homing of naive T lymphocytes to secondary lymphatic organs is probably the best understood of these processes, and information on chemokines in inflammation, asthma, and neurological diseases is rapidly increasing. Over the past 15 years, understanding of the size and functional complexity of the chemokine family of peptide chemoattractants has grown substantially. In this review, we first present information regarding the structure, expression, and signaling properties of chemokines and their receptors. The second part is a systems physiology-based overview of the roles that chemokines play in tissue-specific homing of lymphocyte subsets and in trafficking of inflammatory cells. This review draws on recent experimental findings as well as current models proposed by experts in the chemokine field.

homing; chemoattractants; T cell; B cell; monocyte; neutrophil

CHEMOKINES ARE SMALL CHEMOATTRACTANT peptides that are structurally very similar (189), as are their cognate receptors (130). Many of the proximal signal transduction pathways that are activated after receptor ligation are also very much alike (9, 12). However, the specific expression, regulation, and receptor binding patterns of each chemokine create a functional diversity that allows chemokines to play roles in such disparate processes as organogenesis (120), hematopoiesis (94), neuronal communication with microglia (76), and leukocyte trafficking (41).

Chemokines may have originated from proteins with essential intracellular functions (186) through gene duplication and selected mutation at a relatively recent evolutionary stage (203). Some chemokines and their receptors may have evolved to fight specific infections (130). Conversely, some microorganisms such as the human immunodeficiency virus-1 (112) or herpesviruses (184) have evolved mechanisms to exploit the chemokine system to promote their survival in the host. Dysregulation of chemokines and chemokine receptors has also been implicated in various autoimmune conditions (7), further emphasizing the importance of understanding the physiological roles of this complex network of molecules.

The chemoattractant property of chemokines was first demonstrated in a chemotaxis assay for neutrophils using interleukin-8 (IL-8) (200), and pertussis toxin-sensitive G protein-coupled receptor signaling was later shown to be required for this effect (129, 191). Soon after their discovery, some chemokines were found to be induced at sites of inflammation and required for proper recruitment of leukocytes to various tissues (10, 11). The goal of this review is to provide a current understanding regarding the roles of chemokines and their receptors in leukocyte recruitment to specific tissues under normal physiological conditions as well as in models of inflammation and disease.

STRUCTURE

Chemokines (Table 1) are highly basic proteins of 70–125 amino acids with molecular masses ranging from 6 to 14 kDa (94). Most are secreted, although some, such as fractalkine, are expressed on the cell

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Table 1. *Characteristics of chemokines*

Systematic Name*	Human Common Names	Mouse Common Names	Receptors Bound	Chemokine Type	Expression	Proposed Functional Expression Sites
CXCL1	GROα, MGSA	MIP-2, KC	CXCR2	ELR+	Inducible	Neutrophilic inflammatory sites; atherosclerotic lesions
CXCL2	GROβ, MIP-2α	KC	CXCR2	ELR+	Inducible	
CXCL3	GROγ, MIP-2β	KC	CXCR2	ELR+	Inducible	
CXCL4	PF4	PF4		ELR−		
CXCL5	ENA-78	LIX	CXCR2	ELR+	Inducible	Neutrophilic inflammatory sites
CXCL6	GCP-2	CKα-3	CXCR1,2	ELR+	Inducible	Neutrophilic inflammatory sites
CXCL7	NAP-2		CXCR2	ELR+	Inducible	Neutrophilic inflammatory sites
CXCL8	IL-8		CXCR1,2	ELR+	Inducible	Neutrophilic inflammation; liver, acute lung injury; atherosclerotic lesions
CXCL9	Mig	Mig	CXCR3	ELR−	Inducible	Th1 inflammation; CNS, intestinal lesions
CXCL10	IP-10	IP-10, CRG-2	CXCR3	ELR−	Inducible	
CXCL11	I-TAC		CXCR3	ELR−	Inducible	Th1 inflammation
CXCL12	SDF-1	SDF-1	CXCR4	ELR−	Constitutive	Bone marrow; thymus; lung; lymphoid organs
CXCL13	BLC, BCA-1	BLC, BCA-1	CXCR5	ELR−	Constitutive	Lymphoid follicles
CXCL14	BRAK, bolekine			ELR−		
CXCL15		lungkine		ELR−		
CXCL16	CXCL16	CXCL16	CXCR6	ELR−, TMD+		Th1 inflammation
CCL1	I-309	TCA-3	CCR8	4 cysteines	Inducible	Th2 inflammation
CCL2	MCP-1, MCAF	JE	CCR2	4 cysteines	Inducible	Th1 inflammation; liver, CNS, allergic lung injury; atherosclerotic lesions
CCL3	MIP-1α	MIP-1α	CCR1,5	4 cysteines	Inducible	Th1 inflammation; lung, CNS, atherosclerotic injury
CCL4	MIP-1β	MIP-1β	CCR5,8	4 cysteines	Inducible	
CCL5	RANTES	RANTES	CCR1,3,5	4 cysteines	Inducible	Th1, Th2 inflammation; Lung, CNS, skin injury; atherosclerotic lesions
CCL6		MRP-1		4 cysteines		
CCL7	MCP-3	MARC	CCR1,2,3	6 cysteines	Inducible	Th1, Th2 inflammation; CNS, lung injury
CCL8	MCP-2	MCP-2	CCR3	4 cysteines	Inducible	
CCL9		MRP-2, MIP-1γ		6 cysteines		
CCL10		CCF18		4 cysteines		
CCL11	eotaxin	eotaxin	CCR3	4 cysteines	Inducible	Th2 inflammation; allergic lung, skin disease
CCL12		MCP-5	CCR2	4 cysteines	Inducible	Th1, Th2 inflammation; allergic lung disease
CCL13	MCP-4		CCR2,3	4 cysteines	Inducible	
CCL14	HCC-1, CKβ1		CCR1	4 cysteines		
CCL15	HCC-2, Lkn-1, MIP-5		CCR1,3	6 cysteines		
CCL16	HCC-4, LEC, Mtn-1	LCC-1	CCR1	4 cysteines		
CCL17	TARC	TARC	CCR4	4 cysteines	Inducible	Th2 inflammation in skin
CCL18	DC-CK1, PARC			4 cysteines	Constitutive	Lymphoid T cell zones
CCL19	MIP-3β, ELC, ckβ11	MIP-3β, ELC	CCR7	4 cysteines	Constitutive	Lymphoid T cell zones
CCL20	MIP-3α, LARC	MIP-3α, LARC	CCR6	4 cysteines	Constitutive	Intestinal villi; skin
CCL21	6Ckine, SLC, ckβ9	SLC, TCA-4	CCR7	6 cysteines	Constitutive	Lymphoid organs, HEV
CCL22	MDC, STCP1	abcd-1	CCR4	4 cysteines	Both	Thymus; allergic lung disease; Th2 inflammation
CCL23	MPIF-1, ckβ8-1		CCR1	6 cysteines		

Continued

Table 1.—*Continued*

Systematic Name*	Human Common Names	Mouse Common Names	Receptors Bound	Chemokine Type	Expression	Proposed Functional Expression Sites
CCL24	MPIF-2, eotaxin-2		CCR3	4 cysteines	Inducible	Th2 inflammation
CCL25	TECK, ckβ15	TECK, ckβ15	CCR9	4 cysteines	Constitutive	Small intestine; thymus
CCL26	eotaxin-3, MIP-4α		CCR3	4 cysteines	Inducible	Th2 inflammation
CCL27	CTACK, ILC, ESkine	ALP, skinkine	CCR10	4 cysteines	Constitutive	Skin
CX_3CL1	fractalkine	neurotactin	CX_3CR1	TMD^+	both	Ubiquitous
XCL1	lymphotactin, ATAC	lymphotactin	XCR1			

*Systematic nomenclature and mouse/human correlation defined by Zlotnik and Yoshie (203). GRO, growth-related oncogene; MGSA, melanoma growth stimulatory activity; MIP, macrophage inflammatory protein; PF, platelet factor; ENA, epithelial cell-derived neutrophil-activating factor; LIX, lipopolysaccharide-induced CXC human chemokine; GCP, granulocyte chemotactic protein; CK, chemokine; NAP, neutrophil-activating protein; IL, interleukin; Mig, monokine induced by γ-interferon; IP-10, γ-interferon-inducible protein; CRG, chemokine responsive to gamma; I-TAC, interferon-inducible T-cell chemoattractant; SDF, stromal cell-derived factor; BCA-1, B-cell-activating chemokine; BLC, B-lymphocyte chemoattractant; BRAK, breast and kidney expressed chemokine; TCA, T-cell-activation protein; MCP, monocyte chemoattractant protein; MCAF, monocyte chemotactic and activating factor; RANTES, regulated on activation normal T-cell expressed and secreted; MRP, MIP-related protein; CCF, CC chemokine factor; HCC, hemofiltrate CC chemokine; Lkn, leukotactin; LEC, liver expressed chemokine; Mtn, monotactin; LCC, liver-specific CC chemokine; TARC, thymus- and activation-related chemokine; DC-CK, dendritic cell chemokine; PARC, pulmonary- and activation-regulated chemokine; ELC, Epstein-Barr virus-induced receptor ligand chemokine; LARC, liver- and activation-induced chemokine; 6Ckine, 6 cysteine chemokine; SLC, secondary lymphoid tissue chemokine; MDC, macrophage-derived chemokine; STCP, stimulated T-cell chemotactic protein; MPIF, myeloid progenitor inhibitory factor; TECK, thymus-expressed chemokine; CTACK, cutaneous T cell-attracting chemokine; ILC, interleukin 11 receptor alpha-locus chemokine; ESkine, embryonic stem cell chemokine; ALP, amino-terminal alanine-leucine-proline chemokine; KC, JE, I-309, MARC, abcd-1, ATAC, derived from gene names; TMD, transmembrane domain.

surface (86). Although sequence identity (Fig. 1) among chemokines can be quite low (189), the overall tertiary structure is strikingly similar (34). In most situations, chemokines are thought to act as monomers (12). Most chemokines contain at least four cysteines that form two disulfide bonds, one between the first and the third and one between the second and the fourth cysteine (Fig. 2). The resulting structure contains three β-sheets with short loops in a Greek key formation. Chemokines are subdivided into CC, CXC, or CX_3C groups based on the number of amino acids between the first two cysteines. Lymphotactin (93) is the only known chemokine that contains only two cysteines (C chemokine), corresponding to the second and fourth cysteines of other classes. The two regions of each chemokine that interact with the receptor are an exposed loop in the backbone between the second and third cysteine, believed to be required for low-affinity binding of chemokines to their receptors, and the NH_2-terminal portion before the first cysteine, which represents the region of most variability. The NH_2-terminal binding site is required for receptor signaling upon ligation, and the length and amino acid composition of the NH_2 terminus determines whether a chemokine will bind with high affinity to a receptor and whether binding has agonistic vs. antagonistic effects (34). CXC chemokines are further classified according to the presence of the tripeptide motif glutamic acid-leucine-arginine (ELR) in the NH_2-terminal region. ELR+ chemokines are specific for myeloid cells, whereas ELR− chemokines attract a variety of leukocytes.

Chemokine receptors (Table 2) are heptahelical G protein-coupled receptors, typically 340–370 amino acids in length with 25–80% amino acid identity (Fig. 3), and common features including an acidic NH_2 terminus, a conserved 10-amino acid sequence in the second intracellular loop, and one cysteine in each of the four extracellular domains (130). Structures of chemokine receptors have yet to be solved, although their transmembrane domains are likely similar to rhodopsin (115). Homodimers may be the functional form of at least some chemokine receptors (151). The chemokine binding site is complex, involving several noncontiguous sites, including the NH_2-terminal segment (130).

SIGNAL TRANSDUCTION AND CONSEQUENCES OF RECEPTOR LIGATION

The consequences of chemokines binding their receptors have been studied extensively both in vivo and in vitro (12). One effect brought about by all chemokines involves the chemotaxis of the cell expressing the receptor toward areas with higher concentrations of the chemokine. The receptor for chemokines with transmembrane domains like fractalkine may also induce adhesion and migration in a manner analogous to adhesion molecules (86). However, most chemokines are secreted, and to elicit chemotaxis in vivo, these highly basic proteins must be immobilized on cell or extracellular matrix surfaces by interacting with negatively charged glycosaminoglycans. Interestingly,

specific chemokines bind different types of glycosaminoglycans with divergent affinities (101). Glycosaminoglycan type can vary with cell type, location, and inflammatory status. Therefore, selective immobilization at a given site may be a regulatory step that determines chemokine function in certain tissues or inflammatory states. Furthermore, oligomerization of chemokine occurs on glycosaminoglycans and may provide a mechanism for gradient formation (81). Chemokines near their sites of production may form higher order oligomers on endothelial or extracellular matrix glycosaminoglycans, thereby creating and preserving higher concentrations of chemokine near the initiating inflammatory or trafficking stimulus that cause the leukocyte to move up the chemokine gradient and toward the relevant site.

Other effects are more specific to certain chemokines and include cellular shape changes (Fig. 4), extension of lamellipodia through cytoskeletal restructuring, and release of oxygen radicals, histamine, and cytotoxic proteins from neutrophils, basophils, and eosinophils, respectively (9). Certain chemokines can trigger inte-

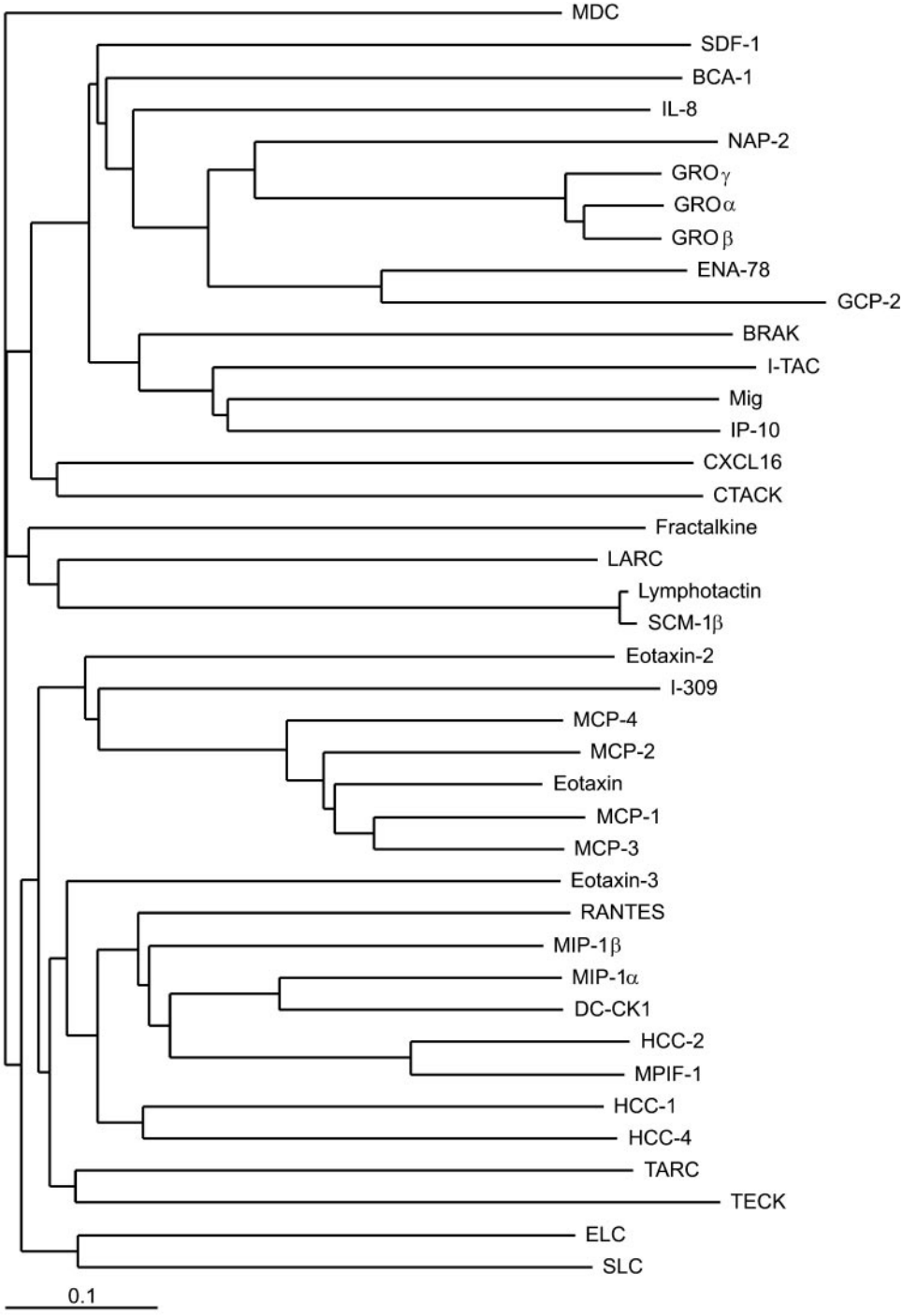


Fig. 1. Dendrogram showing the amount of protein sequence similarity among all known human chemokines. Protein sequences were obtained from the National Center for Biotechnology Information protein database. The phylogenetic tree was constructed using the Clustalw program provided by the European Bioinformatics Institute and analyzed using TreeView (139). The scale bar reflects the horizontal distance at which sequences diverge by 10% (90% identity). Amino acid identity between a pair of chemokines is given by $1 - x$, where x is the sum of the 2 horizontal distances to the right of the pair's vertical branch point. For example, the horizontal distances before the vertical branch point of monocyte chemoattractant protein (MCP)-1 and MCP-3 are 13.6 and 12.4%, respectively. Therefore, the amino acid identity between these chemokines is $100 - (13.6 + 12.4)\%$ or 74%. MDC, macrophage-derived chemokine; SDF, stromal cell derived factor; BCA, B cell-activating chemokine; IL, interleukin; NAP, neutrophil-activating protein; GRO, growth-related oncogene; ENA, Epithelial cell-derived neutrophil-activating factor; I-TAC, interferon-inducible T cell chemoattractant; Mig, monokine induced by γ-interferon; IP, inducible protein; CTACK, cutaneous T cell attracting chemokine; LARC, liver- and activation-induced chemokine; RANTES, regulated on activation normal T cell expressed and secreted; MIP, macrophage inflammatory protein; DC, dendritic cell; HCC, hemofiltrate cc chemokine; MPIF, myeloid progenitor inhibitory factor; TARC, thymus- and activation-related chemokine; TECK, thymus-expressed chemokine; ELC, Epstein-Barr virus-induced receptor ligand chemokine; SLC, secondary lymphoid tissue chemokine.

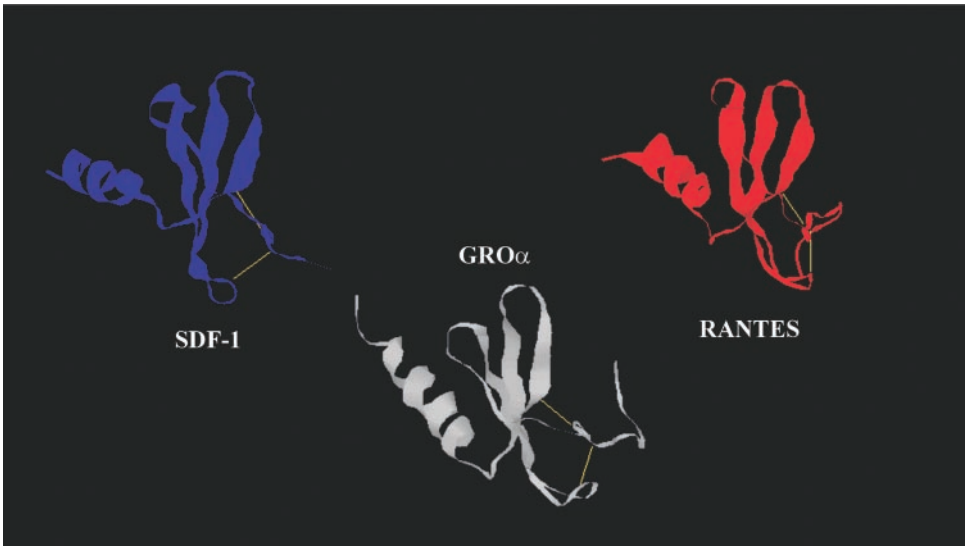


Fig. 2. Comparison of the 3-dimensional structures of human CXC homeostatic [stromal cell-derived factor (SDF)-1], CXC inflammatory (GROα), and CC inflammatory (RANTES) chemokines. Each chemokine is displayed with NH_2 terminus on the *right* and COOH-terminal α-helix to the *left*. The 2 disulfide bonds are also shown. Protein Data Bank files for SDF-1 (ID# 1QG7), GROα (ID# 1MGS), and RANTES (ID# 1RTO) were obtained from the National Center for Biotechnology Information structure database. Files were analyzed using RasWin 2.6-ucb (Roger Sayle, Glaxo Wellcome, Hertfordshire, UK).

grin-dependent firm adhesion of rolling cells, an important step in the trafficking of leukocytes to sites of inflammation (107). IL-8 and monocyte chemoattractant protien (MCP)-1 can trigger β_2-integrin-mediated firm adhesion of monocytes (57) on intracellular adhesion molecule-1 (ICAM-1)-expressing cells in flow chambers. KC, a mouse chemokine related to IL-8, but not JE, mouse MCP-1, triggers arrest of monocytes via

Table 2. *Characteristics of chemokine receptors*

Receptor	High Affinity Ligands	Functional Expression on Immune Cells	Roles in Leukocyte Trafficking
CXCR1	CXCL2,3,5,6,7,8	PMN, mast cells, monocytes, macrophages	Recruitment of myeloid-lineage cells to inflammatory sites including liver, lung, atherosclerotic lesions
CXCR2	CXCL1,2,3,5,6,7,8	PMN, mast cells, monocytes, macrophages	Recruitment of myeloid-lineage cells to inflammatory sites including liver, lung, atherosclerotic lesions
CXCR3	CXCL9,10,11	T cells (Th1 > Th2), B cells, NK	Recruitment of lymphocytes to Th1-type inflammatory sites including CNS, intestine
CXCR4	CXCL12	most progenitor cells, T cells, B cells, PMN, monocytes, macrophages, DC	Bone marrow and follicular B cell emigration; thymocyte homing; early recruitment of T cells to inflamed lung
CXCR5	CXCL13	B cells, memory T cells	Lymphocyte migration to B cell follicles
CXCR6	CXCL16	memory T cells	Recruitment of Th1 cells to inflamed sites
CCR1	CCL3,5,7,14,15,16,23	memory T cells	Recruitment to most types of inflammation including liver, lung, CNS, atherosclerosis
CCR2	CCL2,7,12,13	monocytes, DC, NK, basophils, PMN	
CCR3	CCL5,7,8,13,15,24,26	eosinophils, basophils, mast cells, T cells (Th2 > Th1)	Recruitment to Th2-type inflammatory sites including lung and skin
CCR4	CCL17,22	T cells (Th2 > Th1)	Lymphocyte recruitment to Th2-type inflammatory sites including lung and skin
CCR5	CCL3,4,5	progenitors, Th1 cells, monocytes, macrophages, DC	Recruitment to Th1-type inflammatory sites including CNS, atherosclerotic lesions
CCR6	CCL20	memory T cells, DC	Langerhans-type DC homing to skin
CCR7	CCL19,21	T cells, B-cells, DC	Homing to secondary lymphoid organs
CCR8	CCL1,4	Th2 Cells	T cell recruitment to Th2-type inflammatory sites
CCR9	CCL25	$\alpha_4\beta_7$+ T cells, DC, macrophages, thymocytes	T cell homing to small intestine; thymocyte selection
CCR10	CCL27	CLA+ T cells	T cell homing to skin
CCR11	CCL2,8,13	n.a.	
CX_3CR1	CX_3CL1	PMN, monocytes, NK, T cells	Recruitment to inflammatory sites
XCR1	XCL1,XCL2	T cells	

NK, natural killer cell; DC, dendritic cell; PMN, polymorphonuclear granulocyte; CLA, cutaneous lymphocyte antigen.

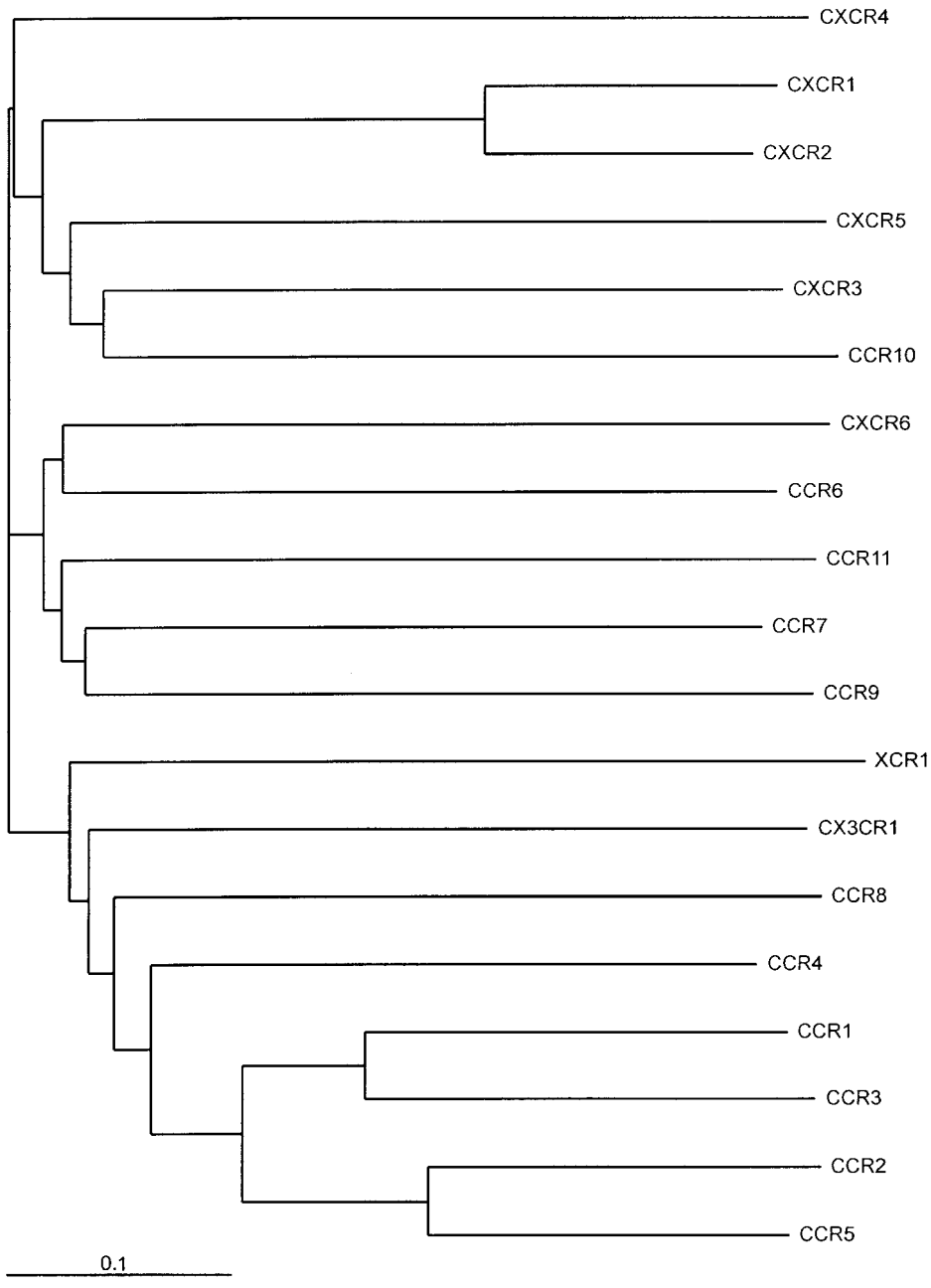


Fig. 3. Dendrogram showing the amount of protein sequence similarity among all known human chemokine receptors. Protein sequences were obtained from the National Center for Biotechnology Information protein database. The phylogenetic tree was constructed using the Clustalw program provided by the European Bioinformatics Institute and analyzed using TreeView (139). The scale bar reflects the horizontal distance at which sequences diverge by 10% (90% identity). Amino acid identity between a pair of chemokine receptors is given by $1 - x$, where x is the sum of the 2 horizontal distances to the right of the pair's vertical branch point. For example, the horizontal distances before the vertical branch point of CXCR1 and CXCR2 are 12.9 and 11.8%, respectively. Therefore, the amino acid identity between these chemokine receptors is $100 - (12.9 + 11.8)\%$ or 75.3%.

$\alpha_4\beta_1$-integrin in atherosclerotic arteries (84). Secondary lymphoid tissue chemokine (SLC), liver- and activation-induced chemokine (LARC), Epstein-Barr virus-induced receptor ligand chemokine (ELC), and stromal cell derived factor (SDF)-1, but not IL-8, MCP-1, regulated on activation normal T cell expressed and secreted (RANTES), eotaxin, macrophage inflammatory protein-1α (MIP-1α), or thymus-and activation-related chemokine (TARC), also trigger firm adhesion of lymphocytes on ICAM-1 (31). SLC is the only known chemokine that can trigger $\alpha_4\beta_7$-integrin-mediated firm adhesion of lymphocytes to mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) (138). Mice lacking CXCR2 show elevated leukocyte rolling velocity (128), suggesting potential involvement of this receptor in slowing down rolling leukocytes via engagement of β_2-integrins before arrest (100).

Most work pertaining to signal transduction events (Fig. 5) downstream from chemokine receptor ligation thus far has focused on neutrophils and interactions between CXCR1, CXCR2, and their respective ligands (9, 12). Except for the receptor desensitization pathways discussed below, most signaling depends on coupling through Bordatella pertussis toxin-sensitive G proteins (20). CXCR1 and CXCR2 couple most commonly through $G\alpha_{i2}$, but also through $G\alpha_{14}$, $G\alpha_{15}$, and $G\alpha_{16}$, but not $G\alpha_q$ or $G\alpha_{11}$ (191). Downstream of G proteins, receptor ligation leads to activation of many

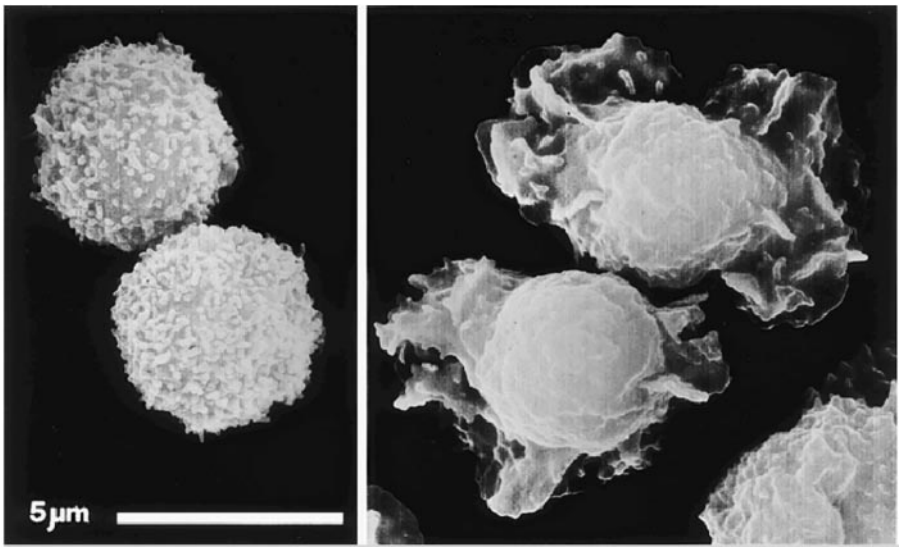


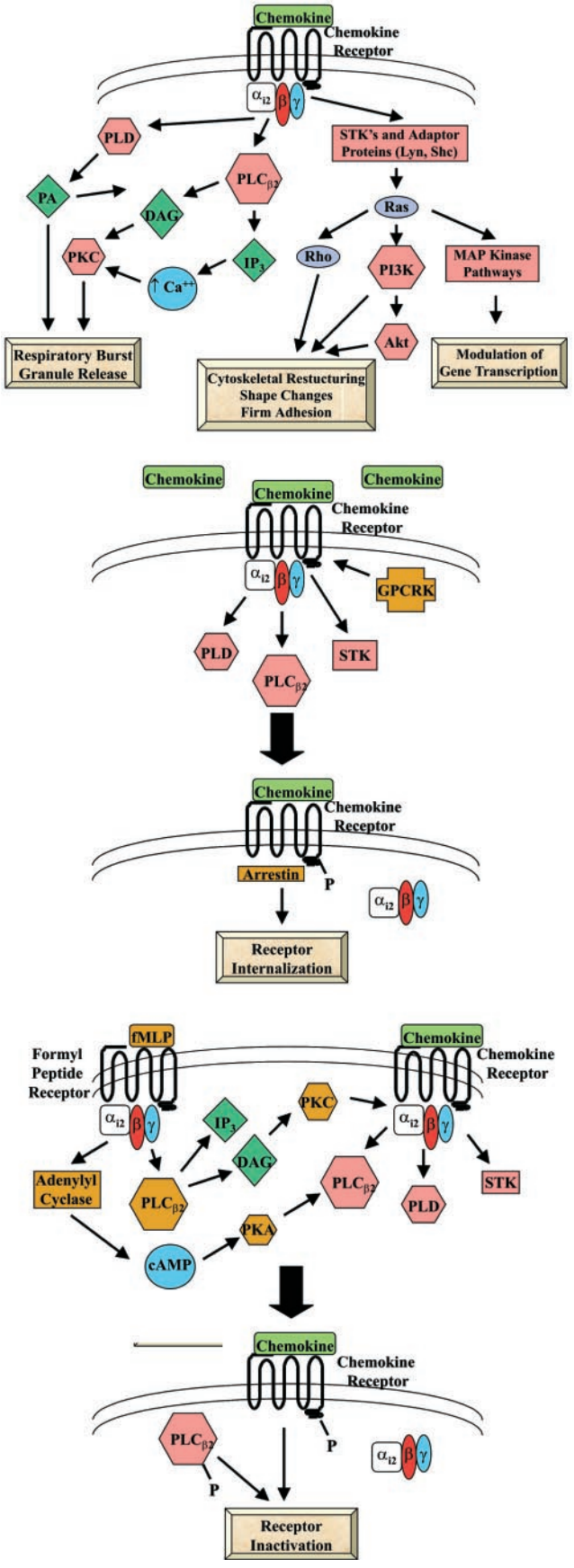
Fig. 4. Electron micrograph showing the shape of human neutrophils before (*left*) and 5 s after (*right*) chemoattractant stimulation. [Reprinted with permission (9)].

intracellular pathways. One consequence of ligation shared by all chemokine receptors with the exception of low affinity receptors such as the Duffy antigen receptor complex (33) is activation of phosphotidylinositol-specific phospholipase C, which through inositol triphosphate and diacylglycerol leads to transient increases in cytosolic free Ca^{2+} through mobilization of intracellular stores of Ca^{2+} and activation of protein kinase C. In neutrophils, both of these steps are required for granule release and superoxide production but not for migration (11). Cytoskeletal restructuring leading to shape changes, firm adhesion, and chemotaxis results from the activation of small GTPases such as Rho (20, 104). CXCR1, but not CXCR2, activates phospholipase D, leading to superoxide formation by human neutrophils (91, 102). MAP kinases such as ERK2 (90), protein kinase B (179), and numerous transcription factors are also upregulated by receptor ligation. Phosphotidylinositol-3-OH kinases (PI3K) are activated by $G_{\beta\gamma}$, small GTPases, SRC-related tyrosine kinase and phosphotyrosines binding the SH2 domain of PI3K (12) and may play key roles in chemokine signal transduction (178, 180), including chemotactic migration (11) and homologous and heterologous desensitization (Fig. 5).

Homologous receptor desensitization occurs when a receptor binds chemokine and is phosphorylated by a G protein receptor-coupled kinase (4, 150). The receptor is subsequently internalized. This mechanism plays a major role in determining the duration of leukocyte trafficking, migration, or sequestration in certain situations (146). Heterologous desensitization occurs without receptor ligation and results from serine phosphorylation of the receptor by a kinase activated by a different signaling cascade (105). One example is the desensitization of CXCR1, CXCR2, CXCR4, and CCR5 through activation of formyl peptide receptors by the tripeptide formylmethionyl-leucyl-phenylalanine (fMLP) (4, 43). Only in some instances is this desensitization accompanied by internalization of the receptor. Unlike homologous desensitization, this pathway is completely inhibited by blocking protein kinase C. The importance of this phenomenon in inflammation and leukocyte trafficking is not completely clear (105), but the capacity for heterologous desensitization appears to be different among chemoattractant receptors, suggesting a hierarchy of chemoattractants (54).

SPECIFICITY AND INTERSPECIES VARIATION

Chemokine and chemokine receptor pairs vary widely in terms of selectivity (Tables 1 and 2). Certain chemokines bind only one receptor and vice versa, such as the exclusive interactions of CXCR4 with SDF-1 (42), CXCR5 with B cell-activating chemokine-1 (BCA-1) (106), CCR6 with LARC (199), CCR9 with thymus-expressed chemokine (TECK) (99), CCR10 with cutaneous T cell attracting chemokine (CTACK) (79), and CXCR6 with CXCL16 (124). Another pattern of pairing involves chemokine receptors that exclusively bind two or three chemokines, as illustrated by CCR7 binding SLC and ELC (197, 198), CXCR3 binding γ-interferon-inducible protein (IP-10), monokine induced by γ-interferon (Mig), and interferon-inducible T cell chemoattractant I-TAC (35, 110), CCR4 binding TARC and macrophage-derived chemokine (MDC) (85), and CCR8 binding TARC and T cell-activation protein-3 (TCA-3) (202). Many other receptors and chemokines are far more promiscuous. CCR3 for instance has been shown to bind eotaxin, eotaxin-2, eotaxin-3, MCP-2, MCP-3, MCP-4, and RANTES (9). RANTES has been shown to bind at least CCR1, CCR3, and CCR5 with high affinity (130). There are also chemokines such as lungkine (152) and dendritic cell chemokine-1 (DC-CK1) (1) that exert their effects through as yet unidentified receptors. In general, chemokines and receptors that are involved in inflammatory trafficking



and activation of cells tend to participate in overlapping and redundant pairing, whereas those involved in homeostatic homing tend to show more exclusive interactions. Chemokines from the same gene cluster all tend to bind the same or similar receptors. The genes for many inducible inflammatory CC chemokines are on human chromosome 17, all of the ELR+ CXC chemokines are on chromosome 4, ELC and SLC are on chromosome 9, and MDC and TARC are on chromosome 16 (130).

The relatively late evolutionary appearance of chemokines resulted in a large amount of chemokine and receptor variation among species. Although CXCR1 is thought to play a pivotal role in neutrophil recruitment in humans (11), it does not appear to have a homolog in mice, and whereas a homologous protein is present in rats, it is expressed on macrophages and not neutrophils (130). Human chemokines for which a mouse homolog has not yet been discovered include IL-8, neutrophil-activating protein-2 (NAP-2), I-TAC, MCP-4, hemofiltrate CC chemokine-1 (HCC-1), myeloid progenitor inhibitory factor-1 (MPIF-1) and -2, and eotaxin-2 and -3, whereas mouse chemokines with no human counterpart include MIP-related protein-1 (MRP-1) and -2, lungkine, and MCP-5 (203). Findings in animal studies, though often very beneficial to understanding human chemokine and receptor actions, should therefore be interpreted cautiously.

EXPRESSION PATTERNS

Chemokines are typically expressed in one of two characteristic patterns (Table 1). Chemokines involved in homeostatic trafficking such as SDF-1, BCA-1, SLC, ELC, CTACK, and TECK are expressed constitutively by many cell types in tissue-specific sites and contribute to homeostatic homing in these areas as discussed in detail below. The expression of inflammatory chemokines, in contrast, is induced only under specific conditions, typically by inflammatory cytokines. In general, lipopolysaccharide (LPS), IL-1β, and tumor necrosis factor (TNF)-α induce broad expression of inflammatory chemokines by a variety of cell types,

Fig. 5. Overview of the major intracellular signaling events induced by a chemokine binding to its receptor and activating responses in a neutrophil (*top*). In response to strong or prolonged chemokine stimulus, the receptor undergoes homologous desensitization (*middle*), in which phosphorylation by a G protein-coupled receptor kinase leads to (thick arrow) uncoupling of G proteins, binding of arrestins, and subsequent internalization of the receptor. Heterologous desensitization (*bottom*) occurs through activation of protein kinase C and protein kinase A by another chemoattractant, leading to (thick arrow) phosphorylation of the receptor and phospholipase $C_{\beta 2}$, respectively, and the subsequent inactivation, but not internalization, of the receptor. $\alpha_{i2}\beta\gamma$, G-protein subunits; PLD, phospholipase D; PLC$_{\beta 2}$, phospholipase C isoform β2; STK, soluble tyrosine kinase; PA, phosphatidic acid; DAG, diacylglycerol; PKC, protein kinase C; IP$_3$, inositol triphosphate; PI3K, phosphotidylinositol 3-kinase; Akt, protein kinase B; GPCRK, G-protein-coupled receptor kinase; fMLP, formylmethionyl-leucyl-phenylalanine; cAMP, cyclic adenine monophosphate, MAP kinase, mitogen-activated protein kinase; Ras and Rho, small G proteins; P, phosphate.

whereas other inflammatory mediators induce more specific responses (172). T-helper 1 (Th1)-like responses produce inflammatory reactions characterized by interactions between macrophages, neutrophils, and type-1 helper T cells that produce the cytokines IFN-γ and IL-12. Th2 responses produce allergic reactions involving eosinophils, mast cells, basophils, and type-2 helper T cells that produce the cytokines IL-4 and IL-13 (184). IFN-γ induces expression of a number of chemokines that act to recruit monocytes, neutrophils, and Th1 lymphocytes, while IL-4 and IL-13 induce MCP-1, eotaxin, TCA-3, TARC, and MDC, which lead to a Th2 pattern of cell recruitment. IL-4 and IFN-γ can antagonize each other's chemokine induction (23). Only activated effector lymphocytes usually respond to inflammatory chemokines, because naive cells typically do not express receptors for these chemokines (172).

Chemokine receptors fall loosely into two categories of expression, those expressed exclusively on a small number of leukocyte types and those that are more broadly expressed. CXCR4, present on T cells, B cells, monocytes, neutrophils, blood-derived dendritic cells, and others, is the most widely expressed chemokine receptor. CXCR1 and CXCR2 are expressed on most leukocytes but appear to be functionally significant only for neutrophils, monocytes/macrophages, and mast cells (130, 135). CXCR3, CXCR5, and CXCR6 are expressed exclusively on cells of lymphoid lineage (51, 147, 182). CCR1, CCR2, and CCR4-CCR10 are expressed mainly on lymphocytes, monocytes, and monocyte-derived dendritic cells (130). CCR3 has a unique expression pattern, as it is found on eosinophils, mast cells, basophils, Th2 lymphocytes, and certain dendritic cell populations (155, 161).

Chemokine receptor expression is also regulated by a variety of inflammatory stimuli (172). T cell expression of CCR1, CCR2, and CXCR3 is induced and maintained by IL-2, but inhibited by activation through the CD3 complex (111, 113), whereas CCR3 expression requires the synergistic effects of IL-2 and IL-4 (88). CCR5 is upregulated by Th1 cytokines, but can be suppressed by IL-10 (140), whereas CXCR4 can be upregulated or downregulated by IL-4 or IFN-γ, respectively (5). Transforming growth factor-β decreases CCR1, CCR2, CCR3, and CCR5, whereas it upregulates CCR7. Interferon-α, which induces expression of CCR1 and decreases CCR4, can either increase or decrease CCR3 and CXCR3 expression depending on T cell polarization (160). Activation of cells can also change chemokine expression. For T cells, activation through T cell receptor stimulation triggers a decrease in expression of CCR1, CCR2, CCR3, and CCR5; increased expression of CCR7, CCR8, and CXCR5; and experimental condition-specific changes in levels of CXCR3, CCR4, and CXCR4 (119, 172). Activation leads to decreased CXCR5 on B cells (51), whereas maturing monocyte-derived dendritic cells switch off expression of receptors for inflammatory chemokines and increase expression of lymph node-homing chemokines (162). Thus expression of chemokine receptors is an axis of regulation that can greatly influence leukocyte trafficking patterns.

ROLE OF CHEMOKINES IN TISSUE-SPECIFIC LEUKOCYTE TRAFFICKING

Secondary lymphoid organs. Secondary lymph organs play critical roles in the initiation of immune responses by serving as sites where naive T cells and B cells become activated through interactions with circulating memory cells and maturing dendritic cells arriving from sites of inflammation. These interactions serve as the basis for the selection, proliferation, and reprogramming of antigen-specific B cells and T cells, which enables homing of the correct subtypes of these cells to sites of inflammation where the initiating agent can be contained and destroyed (41). Whether these events occur in lymph nodes, Peyer's patches, the spleen, or in tonsilar tissue depends on the site of antigen encounter by dendritic cells and the presence of region-specific cell surface chemokine receptors and adhesion molecules on leukocytes (28). For instance, expression of the intestine-tropic integrin $\alpha_4\beta_7$ causes naive cells to home selectively to Peyer's patches (74). The chemokine-dependent events (Fig. 6) that mediate cellular interactions may be similar in the various secondary lymphoid organs (27), but there is also evidence for organ specificity (99).

Human immature dendritic cells derived from monocytes express the inflammatory chemokine receptors CXCR1, CCR1, CCR2, and CCR5 (162, 171), which allow these cells to follow chemotactic gradients to inflammatory sites. Once there, dendritic cells process antigen and become exposed to the maturation-stimulating cytokines TNF-α and IFN-γ (158). Maturing dendritic cells express large amounts of MIP-1α and MIP-1β through 3 h postinduction along with IP-10, MCP-2, and RANTES in a more sustained fashion (162). One consequence of this increased chemokine expression is the downregulation of inflammatory chemokine receptors on maturing dendritic cells, particularly CCR1 and CCR5, by homologous receptor desensitization. Although transcriptional regulation may also be involved, posttranscriptional events appear to dominate (163). The second consequence of this upregulation of chemokines is that it strengthens the original chemotactic gradient, further boosting recruitment of immature dendritic cells, monocytes, and T cells and creating a continuous antigen-sampling loop (157). In addition, maturing dendritic cells increase CCR4, CXCR4, and CCR7 expression and ELC/SLC responsiveness in a manner that is resistant to homologous receptor desensitization (158). CCR7 induces dendritic cell migration to secondary lymphatic organs (53). ELC, TARC, MDC, and DC-CK1 are all upregulated by maturing dendritic cells (162), leading to increased interactions with and stimulation of T cells.

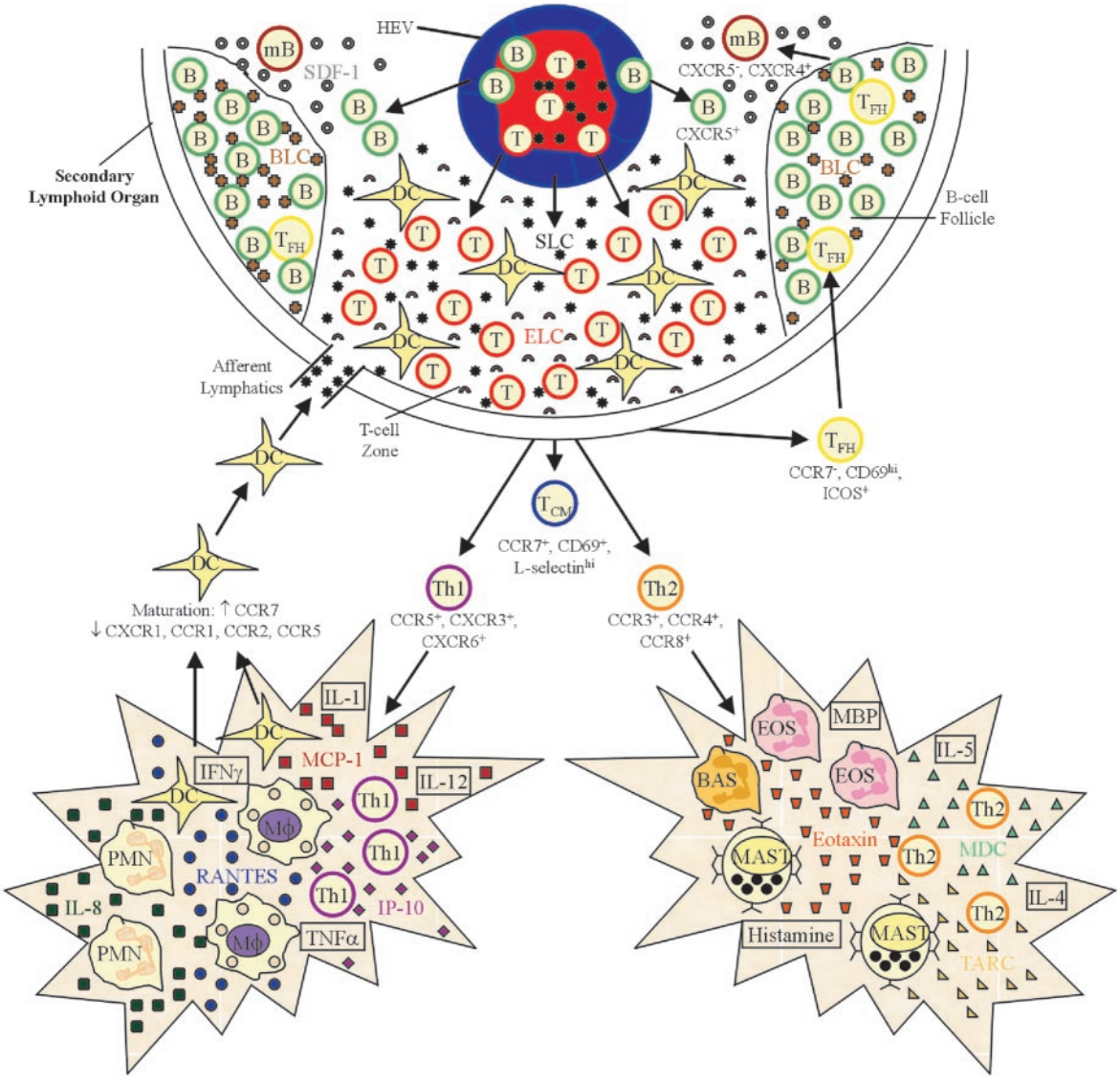


Fig. 6. Chemokine involvement in dendritic cell and lymphocyte trafficking to and from secondary lymphoid organs. Dendritic cells undergoing maturation induced by interferon (IFN)-γ and tumor necrosis factor (TNF)-α lose expression of inflammatory chemokine receptors and increase expression of CCR7, leading to their trafficking to lymphoid organs through afferent lymphatics (*bottom left*). Naive T cells require secondary lymphoid tissue chemokine (SLC) to exit high endothelial venules (*top middle*) and follow SLC and Epstein-Barr virus-induced receptor ligand chemokine (ELC) gradients to T cell zones. At these sites, T cells differentiate into Th1, Th2, circulating memory, and follicular homing cells and the differential chemokine receptors expressed on these subsets produces trafficking to Th1-type inflammation (*bottom left*), Th2-type inflammation (*bottom right*), and B cell follicles, respectively. Naive B cells inside lymphoid organs traffic toward BLC expressed in follicles, whereas mature B cells leave the follicles by migrating toward SDF-1 expressed in the area surrounding the follicles. Chemokines: IP-10 (pink diamond), SDF-1 (open circle), RANTES (blue circle), TARC (yellow triangle), IL-8 (black square), eotaxin (red trapezoid), MCP-1 (red square), MDC (green triangle), SLC (black star), ELC (black half-circle), BLC (red cross). PMN, neutrophil; Mϕ, macrophage; DC, dendritic cell; T, naive T cell; Th1, Th1-type T cell; Th2, Th2-type T cell; T_{CM}, circulating memory T cell; T_{FH}, follicular homing T cell; EOS, eosinophil; BAS, basophil; MAST, mast cell; B, naive B cell; mB, mature B cell; HEV, high endothelial venule; MBP, major basic protein.

Entry of naive lymphocytes into lymph nodes occurs via transmigration across high endothelial venules beginning with a three-step sequential process involving L-selectin-mediated rolling, a chemokine-induced signaling event, and integrin-mediated firm adhesion to the endothelium (27, 184). In vitro experiments have shown that the signaling event required for firm adhesion is mediated by the chemokine SLC binding CCR7 on the surface of naive T lymphocytes (31). CCR7 −/− mice show marked T cell and dendritic cell transmigration defects in lymph nodes and Peyer's patches (53). Similar defects are seen in *plt* mice that lack SLC

expression in lymphoid organs (70). Once inside lymphoid organs, T cells and dendritic cells migrate toward T cell zones in a process that requires CCR7, SLC, and ELC (41). SLC is produced by endothelial cells of lymphoid organs and stromal cells within T cell zones of spleen, lymph nodes, and Peyer's patches (72). ELC is expressed primarily in T cell areas by dendritic cells, macrophages, and other cells (41).

B cell trafficking to secondary lymphoid organs is much less altered by the absence of CCR7 or SLC (53, 70), suggesting other chemokines are involved in triggering firm adhesion of B cells on high endothelial venules. Naive B cells that recirculate to lymphoid organs express high levels of CXCR5 (51), which, through interactions with the chemokine BLC, leads to B cell migration into follicular areas and their subsequent maturation. BLC is produced specifically within B cell areas by stromal cells and follicular dendritic cells (71). CXCR5 −/− and BLC −/− mice have disorganized lymph nodes and decreased antibody responses (6, 52). CXCR5 expression is decreased on activated B cells (51), which may allow their emigration from lymphoid organs. Interestingly, activation of germinal center B cells makes these cells temporarily unresponsive to SDF-1 despite maintaining CXCR4 expression (18). Once B cells are fully mature, responsiveness is regained to SDF-1 expressed in areas surrounding follicles, and thus this regulation may serve as a mechanism to block premature exit of maturing B cells from germinal centers (94).

Within T cell zones of lymph nodes and Peyer's patches, activation leads to the production of polarized sets of T cells. Th1 cells selectively express high levels of CCR5 and CXCR3, although functional CXCR3 is also expressed at low levels on Th2 cells (22, 114). These receptors, along with decreased levels of CCR7, are thought to allow migration of Th1 cells to inflammatory sites where IFN-γ has induced the production of IP-10, Mig, and MIP-1β (119). All Th2 lymphocytes express CCR4 and CCR8, and a subset in humans, but not mice (69), expresses CCR3 (5, 22). IL-4-induced MDC, TARC, TCA-3, and eotaxin can then recruit these cells to sites of allergic inflammation (22, 202). Activation of Th2 cells is also accompanied by markedly decreased CCR7 expression allowing for migration out of T cell zones and into B cell areas where these cells may participate in antibody production (121). Two nonpolarized subsets of T cells, tonsilar and blood follicular homing (T_{fh}) T cells, are also produced on T cell activation in T cell zones. These cells express high levels of CXCR5 while losing expression of CCR7 (26, 165). Tonsilar T_{fh} cells ($CD4^+$, L-$selectin^{lo}$, $CD69^{hi}$) are localized within germinal centers of secondary lymphoid organs and may play a major role in antibody responses by expressing inducible costimulator (ICOS), a molecule that binds the signaling protein B7RP on B cells and induces antibody production (121). Blood T_{fh} ($CD4^+$, $CD69^-$, L-$selectin^+$, $ICOS^-$) regain expression of CCR7, do not possess immediate effector function, and may be analogous to other types of circulating memory cells (159).

Memory T cells are generally grouped into central memory and effector memory T cell populations (158). Central memory cells express L-selectin, CCR1, CCR4, CCR6, and CCR7, while lacking CD69 and immediate effector function. CCR7 allows these cells to migrate through lymphoid organs to participate in activation of naive B and T cells. Effector memory cells are able to produce inflammatory cytokines or exhibit effector function. These cells express combinations of CCR1, CCR3, CCR4, CCR5, CCR6, and CXCR3. $CD4^+$ memory cells can be of either central or effector type, whereas most $CD8^+$ memory cells are of the effector type. Within 6 h of T cell receptor stimulation, effector memory cells lose this chemokine receptor expression and instead express CXCR5, CCR4, CCR7, and CCR8 (156). Naive cells stimulated in the presence or absence of IL-4 and IL-12 become effector memory or central memory cells, respectively (158). Recently, a new chemokine receptor, CXCR6, that is similar in humans and mice (182), has been shown to be induced on in vitro T cells primed in the presence of IL-12 but not IL-4 (95, 122). In blood, some $CD4^+$ and $CD8^+$ cells are CXCR6+. Very few CXCR6+ cells are found in lymph nodes, but large numbers are seen in sites of inflammation. This evidence suggests that CXCR6 may be a marker of effector Th1 and Tc1 cells. CXCR6 binds the chemokine CXCL16, a transmembrane or soluble protein produced by dendritic cells that attracts T cells and natural killer (NK) cells (124).

Lung inflammation. In asthma and animal models of allergic airway disease, many leukocytes, including mast cells, basophils, T cells, eosinophils, and alveolar macrophages, are recruited in tightly controlled spatial and temporal patterns associated with the pathophysiology of these diseases (73, 118). The adult respiratory distress syndrome (ARDS) results from the accumulation of neutrophils within the pulmonary circulation and alveolar spaces via well-studied adhesion molecule-dependent and -independent pathways (44). Chemokines and chemokine receptors are thought to play critical roles in the recruitment, activation, and coordination of leukocytes in both disease processes.

Much information regarding the expression and function of chemokines in allergic airway disease (AAD) has been provided by the ovalbumin-sensitized/challenged AAD model, in which mice are given an intraperitoneal injection of ovalbumin, followed by intranasal challenge starting ~1 wk later (73). Production of chemokines has been measured in broncheoalveolar lavage (BAL) specimens and by immunostaining and in situ hybridization of the interstitium (87). These studies showed chemokine production by a variety of cell types, including alveolar epithelium, endothelium, smooth muscle, alveolar macrophages, and, at least for eotaxin, infiltrating T lymphocytes (73). In this study, Gutierrez-Ramos et al. (73) place chemokines into three groups on the basis of temporal expression. Eotaxin, MDC, and MCP-1 levels correlate with the

accumulation of eosinophils, T cells, and monocytes, respectively. RANTES, MCP-5, and MIP-1 levels increase nonspecifically over the course of inflammation. SDF-1 is expressed constitutively, and levels do not change over time. Interstitial eosinophilia and bronchoalveolar lavage (BAL) eosinophilia are blocked by antagonists to MCP-1, RANTES, and SDF-1 during both sensitization and challenge periods but not during challenge alone. These findings imply central roles for these chemokines in initial leukocyte subset recruitment. Eotaxin blockade decreases all eosinophilia regardless of time of administration. Blockade of MDC and MCP-5 has no effect on BAL eosinophilia but significantly blocks interstitial eosinophilia and consequent airway hyperreactivity and mucous secretion. These findings suggest that MDC and MCP-5 may be necessary to maintain sequestration of eosinophils within lung interstitial tissues (73).

The first cells to be recruited to the lungs during allergic inflammation are mast cells and basophils. MCP-1, MCP-2, MCP-3, RANTES, MIP-1α, and eotaxin, all expressed by various cells in the lung during early stages of inflammation, can recruit mast cells and basophils (118). Furthermore, both MCP-1 and RANTES can activate basophils to release histamine and produce other mediators (37). For example, intratracheal administration of MCP-1 has been shown to increase leukotriene C_4 (LTC_4) levels in BAL and leukotriene production in pulmonary mast cells (29). In the same study, mice deficient in CCR2 expression were shown to have decreased airway resistance and histamine release in a murine model of allergen airway inflammation induced by cockroach antigen. MCP-1 may be critical in the formation of allergic lung inflammation even in the absence of CCR2 (98). Furthermore, eotaxin can interact with MCP-1-activated basophils to increase their expression of IL-4, ensuring that a Th2-type environment is created and enabling subsequent migration of eosinophils and Th2 lymphocytes and the progression of the allergic response (118).

On the basis of studies using adoptive transfer of labeled cells along with neutralizing antibodies to various chemokines, Th2 lymphocyte homing to lungs during acute airway disease appears to sequentially rely on SDF-1, eotaxin, and MDC (73). SDF-1 is expressed constitutively in the lung, and accumulation of CXCR4+ cells always accompanies inflammatory changes within pulmonary tissue (64). Whether these cells represent critical precursors that recruit other leukocytes to produce inflammation or whether these cells home to the lung constitutively is unclear (73). The next phase of the response involves the upregulation of eotaxin by many cells including CXCR4+ Th2 cells and early expression of CCR3 by newly differentiated Th2 cells (108). The influx of more Th2 cells peaks around 4 days after the initial insult, CCR3 is subsequently downregulated, and CCR4 expression by Th2 lymphocytes and MDC expression throughout the lung are increased. CCR4 and MDC are required for maintenance of interstitial Th2 lymphocytes for the duration of the response (108).

Eosinophil accumulation and activation directly leads to allergic airway inflammation, as these cells release a variety of toxic granular proteins and lipid mediators that cause direct damage to alveolar cells and endothelium as well as indirect damage through influencing other physiological regulators (9). The end results of this damage include bronchial smooth muscle contraction, airway hyperreactivity, increased vascular permeability, and mucous hypersecretion. Initial recruitment of eosinophils is thought to be mediated primarily through CCR1/MIP-1α (153) and CCR3 and its many ligands expressed in the lung, including eotaxin, eotaxin-2, RANTES, MCP-3, and MCP-4 (118). Once fully activated and in tissues, however, eosinophils can migrate in response to MIP-1β via CCR5, TCA-3 via CCR8, and MDC in a process that does not involve CCR4 or CCR3 (19, 66).

CCR3 is involved in the initial lung-specific recruitment of mast cells, basophils, eosinophils, and Th2 cells, all four of the cell types that are critical in allergic lung inflammation. Mast cells, basophils, and eosinophils mediate the effector functions, whereas Th2 cells are required to make IgE antibody via IL-4 production and to prime and activate basophils and eosinophils via IL-5 (9). Blocking CCR3 using the decoy ligand Met-RANTES (189) can significantly block most aspects of allergic airway inflammation, including bronchial hyperactivity and $CD4^+$ cell and eosinophil accumulation in the interstitium and broncheoalveolar lavage fluid (65, 189). Blocking MIP-1α and RANTES using antibodies has also been shown to significantly reduce eosinophil accumulation (117). Alveolar macrophages have also been shown to play a role in chemokine-dependent leukocyte recruitment through low affinity IgE receptors (80). In response to large doses of antigen, IgE-dependent activation of these macrophages causes production of IL-8, MCP-1, and MIP-1α leading to the recruitment of neutrophils, eosinophils, and other leukocytes (67).

Although their role in allergic airway disease remains controversial (118), neutrophils are critical for producing the pathophysiology in sudden-onset atypical asthma (103) as well as in ARDS (45). Intratracheal instillation of IL-8 produces large influxes of neutrophils into the lungs in animal models (192). IL-8 is substantially elevated in BAL from patients with acute lung injury, and expression levels are positively correlated to neutrophil influx (103). Blocking IL-8 has been shown to ameliorate reperfusion-induced neutrophil influx within the lung (168). Epithelial cell-derived neutrophil-activating factor (ENA)-78 is stored in mast cells within the lung, and blockade with an antibody results in a large decrease in lung neutrophil accumulation (116). Surprisingly, eotaxin may negatively regulate neutrophil recruitment to the lung by blocking IL-8-mediated neutrophil chemotaxis (118). Eotaxin-deficient mice have increased neutrophil and decreased eosinophil numbers during acute allergic inflammation. The eosinophil deficit is compensated only much later in the response (154).

Leukocyte trafficking in the central nervous system. Leukocyte trafficking to the central nervous system (CNS) during homeostasis, antigen-specific inflammation, or trauma is complicated by the blood-brain barrier, which prevents most leukocytes from entering the CNS. Chemokines play key roles in overcoming this barrier (59). The CNS is unique in that chemokines are critical for the proper execution of many nonimmune functions. Knocking out the genes for SDF-1 or CXCR4 results in mice with an embryonic lethal phenotype, partly because of grossly abnormal organogenesis of the murine cerebellum (120). Fractalkine is expressed by neurons and is believed to bind CX_3CR1 expressed by microglia, although the significance of this binding is unclear (76, 136, 167). Despite the blood-brain barrier, selective subsets of leukocytes can home to the CNS under baseline conditions. CXCR3+ T cells, representing 90% of all $CD3^+$ cells in cerebrospinal fluid (CSF), are seen in small numbers in the absence of inflammation (82), suggesting that this chemokine receptor may be required for T cell passage across the blood-brain barrier.

Multiple sclerosis (MS) is an autoimmune condition in which antigen-specific Th1 cells cross the blood-brain barrier to mediate focal inflammation of the CNS, resulting in a variety of neurological symptoms and deficits (7). CSF levels of IP-10, Mig, and RANTES are increased in patients with MS undergoing active inflammatory demyelination compared with control subjects without disease (170). Consistent with Th1 lymphocytes being a key pathogenic cell type in this disease, CXCR3 is expressed on 99% of T cells that home to leukocyte-rich areas within MS lesions. These cells are attracted by IP-10, which is expressed at high levels in MS lesions (13, 147), perhaps by astrocytes that form the glial limitans (170). $CD8^+$ T cells specific for myelin basic protein (MBP) are recruited by these Th1 cells and subsequently produce more IP-10, along with MIP-1α and MIP-1β, leading to a vicious cycle of T cell recruitment through CCR1, CCR5, and CXCR3 (17, 94). CCR5 is also expressed on many T cells, macrophages, monocytes, and microglia in CSF and active lesions of patients with MS (13, 170). The importance of CCR5 in recruitment of leukocytes during MS is emphasized by the better prognosis of patients with MS homozygous for the CCR5Δ32 mutation, a population including ~1% of all North American Caucasians (82).

Much has been learned regarding chemokine-dependent leukocyte homing to the CNS during inflammation through the experimental autoimmune encephalitis model (EAE), in which mice are given a subcutaneous injection of CNS myelin proteins in complete Freund's adjuvant followed by doses of pertussis toxin to manipulate disease severity and frequency (82). Symptoms, visible inflammation, and CNS-specific chemokine expression are always preceded by initial antigen-specific T cell infiltration into the CNS (61, 92). During initial inflammation, MCP-1, KC, RANTES, TCA3, and IP-10 are all expressed, possibly by astrocytes (149), 2 days before clinical symptoms (63), and these chemokines may play pivotal roles in leukocyte recruitment. In situ hybridization combined with immunocytochemistry for glial fibrillary acidic protein (GFAP), an indicator of the astrocyte reactive stress response known as astrogliosis, shows that IP-10 and MCP-1 colocalize with GFAP-producing astrocytes, implying that astrocytes may have to undergo astrogliosis to produce chemokines (175). As in MS, IP-10 and CXCR3 play critical roles in EAE. Antisense oligonuceotides for IP-10 (190) and anti-CXCR3 antibodies (7) can block mononuclear cell infiltration and disease development. In the relapsing phase of EAE, RANTES and MIP-1α are produced (60) in a temporal fashion that correlates with leukocyte infiltration and disease onset and resolution of the acute attack (175).

In animal models of cortex trauma (82), MCP-1 RNA is elevated 3 h after trauma, before initial infiltration of leukocytes (58). MCP-1/GFAP colocalization studies suggest that this MCP-1 is produced by astrocytes, and in neonatal models where astrogliosis does not occur, no increase in MCP-1 is seen (14). Spinal cord trauma models (82) have shown growth-related oncogene (GROα) to be key in producing neutrophil recruitment within 24 h (125). In the same study, MCP-1, MCP-5, MIP-3α, and IP-10, but not RANTES or MIP-1α, were elevated at later time points, implying that these chemokines may recruit cell types other than neutrophils to sites of spinal cord injury.

Lymphocyte trafficking and inflammation in the gastrointestinal system. The gastrointestinal system contains four spatially distinct populations of lymphocytes located within Peyer's patches, mesenteric lymph node, lamina propria, and epithelial tissue. Lymphocytes homing to any of these compartments express the $\alpha_4\beta_7$-integrin, which binds to MAdCAM-1, an immunoglobulin-like molecule expressed exclusively by mucosal and high endothelial venules (16). Selective localization to one of the four gastrointestinal lymphatic compartments depends on expression of other surface markers. Most intraepithelial lymphocytes express the $\alpha_E\beta_7$-integrin, which can bind E-cadherin expressed on epithelial cells (3). The role of chemokines in regulating homeostatic homing and inflammatory trafficking of cells within this mucosal system is just beginning to be understood (119). SLC is the only chemokine that can trigger $\alpha_4\beta_7$-mediated firm adhesion to MADCAM-1 in flow chambers in vitro (138), and thus by analogy to its role in peripheral lymph nodes, SLC may play a role in homing to Peyer's patches and mesenteric lymph node. The constitutive expression of a number of chemokines by intestinal epithelial cells has been noted (3), although the significance of most of these molecules is unclear. Positioning of chemokines at specific sites in the epithelium may be important. LARC is expressed by cells comprising the villous epithelium, but not by crypt cells, whereas TECK is expressed in the opposite pattern (99, 174). TECK, constitutively expressed selectively by the small intestine, has recently been postulated to play a critical role in homing

to the lamina propria and the epithelium of this organ. All small intestine-homing $CD4^+$ and $CD8^+$ T cells express CCR9, the receptor that exclusively binds TECK (99).

Interestingly, there also appear to be inflammation-specific pathways of T cell trafficking to the gut (119). Under physiological conditions, virtually all lamina propria and intraepithelial lymphocytes express CXCR3, and this expression can be significantly increased in vitro by IFN-γ (46, 169). In the same studies, CXCR3 ligands, IP-10, and Mig were shown to be expressed on intestinal cells in vitro after IFN-γ treatment, and antibodies to these chemokines blocked intraepithelial lymphocyte chemotaxis in epithelial cell-conditioned medium. Thus Th1-type responses leading to the production of IFN-γ may cause intestine-specific homing through induction of chemokines and their respective receptors. This model may be applicable to ulcerative colitis, as IP-10 is expressed at high levels in focal lesions associated with this disease (181), although CCR3+ Th2 cells are also present at these sites (56).

Skin-homing lymphocytes and cutaneous allergies. Skin-homing memory cells express the cutaneous lymphocyte antigen (CLA), which correlates with E-selectin binding of these cells (28). Specific responses to skin allergens are restricted to CLA+ cells (164). Two chemokines are also critical for skin-specific homing. CTACK, a recently discovered chemokine thought to be expressed exclusively in the skin by keratinocytes, selectively attracts CLA+ skin-homing T cells, which presumably express the CTACK receptor CCR10 (127). TARC is expressed in venules in chronically inflamed skin, and its receptor CCR4 is expressed on lymphocytes that infiltrate inflamed skin but not intestine (30). In the same study, TARC was shown to trigger integrin-dependent firm adhesion of CLA+ cells, but not $\alpha_4\beta_7$+ cells, in flow chambers coated with ICAM-1 in vitro, further demonstrating the selective role TARC plays in recruitment of skin-homing cells. Through CCR6 binding, LARC is able to direct the constitutive homing of Langerhans-type dendritic cells to areas of the epidermis, providing resting antigen presenting capability (32).

In inflamed skin lymphatics, the ability of glycosaminoglycans to bind RANTES, MCP-1, and MCP-3, but not MIP-1α or IL-8, is thought to play a role in determining which inflammatory cells are recruited (25, 83). RANTES and MCP-3 recruit CCR3+ Th2 cells in patients with contact dermatitis (56), and these chemokines also activate eosinophils and basophils in vitro, causing their chemotaxis and the release of mediators such as histamine and leukotrienes (10). RANTES may also recruit and activate cutaneous mast cells, as a RANTES antagonist is effective in reducing eosinophilia and swelling by blocking mast cell degranulation (177, 189).

Chemokine-dependent leukocyte recruitment has been studied extensively in atopic dermatitis. The current model postulates that the initial phase of the disease is mediated by antigen-specific Th2 cells that produce local inflammation. These cells use chemokines to subsequently recruit eosinophils and macrophages, which then produce cytokines such as IL-12 that induce a switch to a Th1-type response (68). Eighty-five percent of T cells in skin inflammatory infiltrates are CLA+ (143). Eotaxin expression by resident mononuclear cells may be the key step in recruiting CCR3+ Th2 cells and later eosinophils (80). T cell expression of eotaxin and CCR3 appears to be greatly elevated in patients with atopic dermatitis vs. normal controls, whereas there are no differences in MCP-3, MIP-1α, and IL-8 (195). RANTES is also increased in atopic lesions (166), although peak expression occurs at 24 h, much later than the peaks of chemokines that initially attract Th2 cells (196). Late expression of RANTES may help facilitate the switch from a Th2- to a Th1-type response, as RANTES can attract Th2 cells via CCR3 and Th1 cells via CCR5 (80).

Bone marrow. SDF-1 is expressed at high levels by stromal cells in bone marrow (176). Mice deficient in SDF-1 or its receptor CXCR4 do not survive past the first week in utero and have profound defects in hematopoiesis, particularly B cell lymphopoiesis and myelopoiesis (120, 131). Whereas in humans SDF-1 is thought to attract B cells in all stages of development, mouse SDF-1 only attracts pro- and pre-B cells (42). The current model is that SDF-1 may be important in directing B cells to proper sites of maturation within the bone marrow microenvironment, and the loss of SDF-1 responsiveness after maturation allows exit of mature B cells into the circulation (9). ELC and SLC have recently been shown to attract pre-B cells after CD34 expression is downregulated and before IgM is upregulated. CCR7 and its ligands may therefore also be important in allowing B cell emigration from bone marrow (96).

Thymus. In the thymus, dendritic cells involved in negative selection express MDC and TECK, and stromal cells have been shown to express TARC, SDF-1, LARC, SLC, and ELC (94). TECK attracts thymocytes, macrophages, and dendritic cells in the thymus and may assist in negative selection by attracting macrophages to destroy double positive ($CD4^+$, $CD8^+$) thymocytes that are bound by dendritic cells with high avidity (183). SDF-1 may direct homing within the thymus of the more immature thymocyte populations, as it selectively attracts triple negative ($CD3^-$, $CD4^-$, $CD8^-$), double negative ($CD3^+$, $CD4^-$, $CD8^-$), and double positive thymocytes. In contrast, ELC selectively attracts the more mature single positive ($CD4^+$ or $CD8^+$) thymocyte population in the medulla and may aid in their migration into the circulation (97). MIP-1β, which binds CCR5 and CCR8, attracts double positive or single positive thymocytes and may be involved in differentiation of $CD8^+$ or $CD4^+$ subsets, as double positive and $CD8^+$ thymocytes express the MIP-1β receptor CCR5, whereas $CD4^+$ thymocytes are attracted to this chemokine via CCR8 (94). MDC, LARC, and SLC are expressed in thymus but do not attract immature thymocytes. These chemokines may be re-

sponsible for negative feedback of T cell production mediated by circulating mature cells. (94)

Liver. Specialized resident NK 1.1+ T cells and Kupffer cells home to the liver constitutively by as yet unknown mechanisms. In acetaminophen-induced liver toxicity (APAP), MCP-1 is expressed at high levels, potentially by Kupffer cells (21). CCR2 −/− mice develop substantially more injury than do wild-type mice, and this susceptibility can be ameliorated by blocking TNF-α or IFN-γ (78), suggesting MCP-1 and CCR2 may have protective functions during this type of oxidative injury. Fractalkine is also expressed by Kupffer cells in APAP, and fractalkine −/− mice show decreased neutrophil infiltration, serum aspartate aminotransferase (AST), and overall injury (21). ELR+ CXC chemokine administration usually leads to increased infiltration of inflammatory cells but decreases APAP injury due to direct proliferative effects on hepatocytes (77). These effects may also be required for hepatic regrowth in partial resection models (36). Ischemia/reperfusion models, unlike APAP models, have shown that MCP-1 is increased by reactive oxygen species and may produce injury by increasing ICAM-1 expression on hepatic endothelium (194). Reducing this chemokine decreases subsequent injury (193), suggesting that reperfusion-induced inflammation and subsequent oxygen radical production may occur by a mechanism distinct from that of APAP. In chronic alcoholic liver disease and cirrhosis (21), MCP-1 is required for infiltration of monocytes and subsequent inflammation and fibrosis, and expression levels correlate with AST levels and severity of injury (2, 50, 123). IL-8, MCP-1, and MIP-2 are produced by ethanol-challenged hepatocytes in rats and are linked to increased ICAM-1 and vascular cellular adhesion molecule-1 (VCAM-1) expression, both of which are required for neutrophil infiltration (132, 142). T cell migration during chronic hepatitis appears to be selectively controlled by liver expression of IP-10 (173), suggesting that the infiltrating cells may have a Th1 phenotype.

Atherosclerosis and vasculitis. Chemokines are also involved in site-specific homing of leukocytes to atherosclerotic plaques. RANTES, released by thrombin-stimulated platelets, is present on the luminal surface of carotid arteries of apolipoprotein E-deficient mice with early atherosclerotic lesions, and this chemokine along with KC, but not MCP-1, can trigger monocyte arrest on atherosclerotic endothelium in an ex vivo-perfused carotid artery model (84, 185). The formation of a plaque is believed to begin through accumulation of minimally modified low-density lipoproteins (MM-LDL), which become trapped in the extracellular matrix of subendothelial spaces and stimulate endothelial cells and smooth muscle cells to produce MCP-1 and IL-8 (40). KC, a murine chemokine related to human IL-8 and GRO-α, triggers arrest of rolling monocytes in atherosclerotic arteries (84). Subsequent transmigration of large numbers of monocytes into the subendothelial space can be blocked by high-density lipoproteins (HDL), antioxidants, or anti-MCP-1 antibodies (133). Apolipoprotein E-deficient mice lacking CCR2 show smaller lesion sites than apolipoprotein E-deficient control mice (24). Once monocytes are present, MM-LDL are oxidized and taken up by monocytes, creating foam cells that produce MCP-1, IL-8, MIP-1α, MIP-1β, and RANTES (187). These chemokines promote migration of CCR2+ and CCR5+ macrophages and lymphocytes into the plaque. Many of these chemokines have other, pleiotropic effects within plaques (187). MCP-1 induces proliferation of smooth muscle cells (145), whereas IL-8 is mitogenic and chemotactic for smooth muscle cells (201). IP-10, also expressed at high levels in plaques, attracts lymphocytes via CXCR3, but also attracts and leads to the proliferation of smooth muscle cells (188). RANTES, thought to be important in typical plaque formation by recruiting lymphocytes, has been shown to be required in variants such as transplantation-associated accelerated atherosclerosis (141).

Wegener's granulomatosis is a disease characterized by a systemic necrotizing vasculitis likely caused by cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) that recognize a proteinase expressed on the surface of TNF-α-primed neutrophils and monocytes (15). IL-8 may play a key role in the pathogenisis of this vasculitis, as cANCA has been shown to greatly increase IL-8 expression by TNF-primed peripheral blood monocytes (148). RANTES has been localized to Wegener's lesions and therefore may also play a role (39). IL-8 expression is also significantly increased by neutrophils and mononuclear cells isolated from patients with systemic vasculitis due to Kawasaki disease (8). Serum RANTES levels correlate closely with disease activity in Takayasu arteritis (137). MCP-1 is present in the vessel wall and plasma MCP-1 levels are significantly elevated in patients with temporal arteritis and polymyalgia rheumatica (47). In a rat model of chronic adjuvant-induced vasculitis, infusion of MCP-1 produces a large increase in neutrophil transendothelial migration (89), suggesting that MCP-1 may play a critical role in the development of vascular lesions.

Other diseases. Chemokine-dependent inflammation in other tissues is just beginning to be understood. Fractalkine has been shown to induce glomerulonephritis (48), whereas MetRANTES and MIP-2 antibodies have been shown to be effective in treating this disease (49, 109). Interestingly, RANTES expression in the kidney is downregulated by activation of NO production pathways (94). MetRANTES can also block inflammation in collagen-induced arthritis, a murine model of rheumatoid arthritis (144). IP-10 levels are high in rheumatic fluid, as are the levels of CXCR3+ and CCR5+ Th1 cells, but not CCR3+ Th2 cells (56). Coxsackie virus-induced myocarditis appears to involve MIP-1α (38), implying that there are important roles for chemokines in heart pathology as well. Chemokines are also thought to play critical roles in acute allograft rejection (134). Expression of CXCR3, CXCR4, and CCR5 was upregulated on circulating and graft-

infiltrating lymphocytes after liver transplantation (62). The presence of CXCR3 and IP-10 correlated strongly with acute rejection of human cardiac allografts (126). CXCR3 −/− and CCR5 −/− mice or mice treated with neutralizing antibodies to either of these receptors appear to be resistant to the development of cardiac allograft rejection (55, 75).

FUTURE DIRECTIONS

Because of the structural and functional differences of chemokines between humans and rodents (203), the development of animal models that are true representations of human conditions is challenging. Another challenge is the production of antibodies and small molecule inhibitors of chemokine receptors and chemokines (146). Data obtained with these reagents would complement data from knockout animals to help determine causal relationships between chemokines and certain homing patterns in homeostasis and inflammation. Much more work needs to be done to understand constitutive lymphocyte homing pathways, particularly for lung, liver, spleen, the gastrointestinal system, and the CNS. Due to the redundancy of the chemokine system, further understanding of general intracellular events produced by chemokine receptor ligation is necessary to understand how cell movement toward a chemotactic gradient is regulated and how chemokines interact with other classes of chemoattractants and their receptors. This knowledge would allow development of therapeutic interventions at the signaling level that may be broadly applicable to large sets of chemokines and their receptors, thereby producing better clinical outcomes in complex inflammatory diseases.

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