

# The Chemokine Superfamily Revisited

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The chemokine superfamily consists of a large number of ligands and receptors. At first glance, this family appears redundant and their ligand-receptor relationships promiscuous, making its study challenging. However, analyzing this family from the evolutionary perspective greatly simplifies understanding both the organization and function of this apparently complex system. In particular, the functions of a subgroup of chemokines (designated homeostatic chemokines) have played pivotal roles in advancing our understanding of the organization and function of the cellular networks that shape the immune system. Here, we update the full scope of the human and mouse chemokine superfamilies and their relationships and summarize several important roles that homeostatic chemokines play in the immune system.

## Introduction

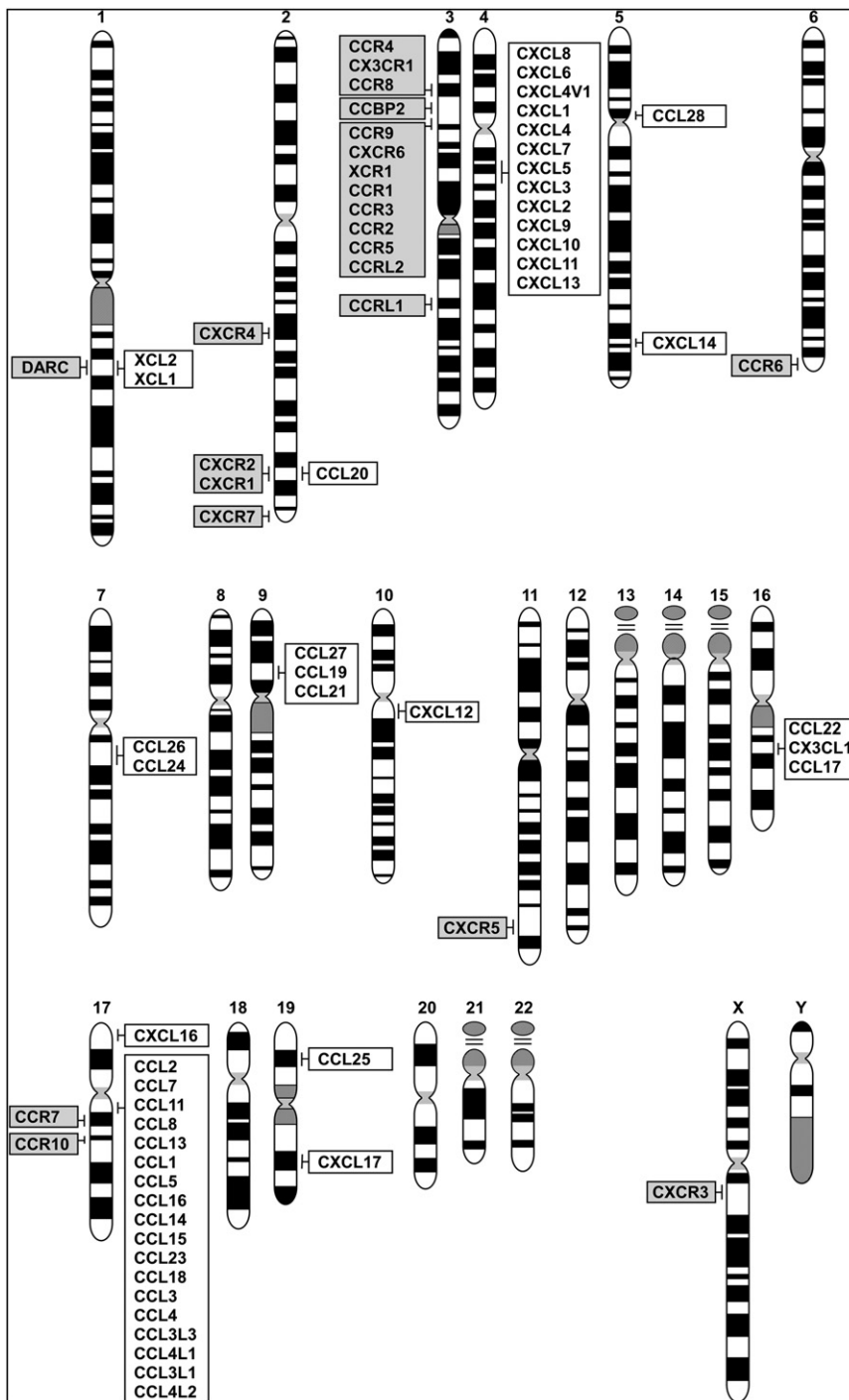
Since the identification of the chemokines CXCL8 (IL-8) and CCL2 (MCP-1) in the late 1980s, the chemokine superfamily has expanded rapidly (Rollins, 1997; Yoshie et al., 2001; Zlotnik and Yoshie, 2000; Zlotnik et al., 2006). An initial wave of chemokine discovery occurred in the early 1990s, when some chemokines that attracted neutrophils and monocytes were discovered. Their identification was facilitated by the abundance of their transcripts in activated cells that participate in inflammatory responses. Their receptors were soon identified and were found to be a subgroup of class A G protein-coupled receptors (GPCRs) (Vassiliatis et al., 2003). However, the initial ligand-receptor relationships that were described were found to be promiscuous: a single chemokine binds to several chemokine receptors, whereas a single chemokine receptor has multiple chemokine ligands. Moreover, the chemokine genes were found to map to two discrete chromosomal sites, thus forming two large gene clusters, one for CXC chemokines (in human, 4q13.3) and another for CC chemokines (in human, 17q12) (Figure 1). Such unorthodox features of the chemokine system along with their innate immunity roles attracted little attention from immunologists during these early years. Most of these chemokines are now classified as inflammatory, because they play pivotal roles in controlling leukocyte recruitment during inflammatory responses.

However, a “second round” of chemokine identification started in the mid 1990s, facilitated by rapidly expanding EST (expressed sequence tag) databases. In contrast to the inflammatory chemokines, the expression of these chemokines is constitutive and restricted to specific cells or organs. Moreover, in contrast to inflammatory chemokines that mainly attract macrophages or neutrophils, they are chemotactic for subsets of lymphocytes or dendritic cells, cells that mediate acquired immunity. Indeed, many were found to play pivotal roles in immune responses and in defining the cellular organization of organs of the immune system. Their receptors also revealed far less promiscuous interactions. In fact, many of them exhibit highly restricted ligand-receptor relationships. In both the human and mouse genomes, the genes encoding homeostatic chemokines are located outside the familiar CXC and CC chemokine

clusters (Figure 1). These findings have led to a paradigm shift in our concept of chemokine function. The functional characterization of these second-round chemokines led to major advances in our understanding of the function and organization of the immune system. It became apparent that many homeostatic chemokines play major roles in the organization of the immune system and are indeed “master regulators” of the movement and localization of lymphocyte and dendritic cell subsets in the body (Moser et al., 2004; Zlotnik et al., 2006). In this review, our objectives include updating the classification and nomenclature of the chemokine superfamily, including the clarification of some nomenclature issues concerning human and mouse chemokines. We also summarize recent developments concerning functions of this interesting gene family in the immune system and, finally, we comment on its potential to yield therapeutics or biomarkers of human disease.

## Chemokine Nomenclature Updated

In our previous review (Zlotnik and Yoshie, 2000), we proposed a systematic nomenclature of the chemokines that originated at the Keystone symposium on Chemokines and Chemotactic Receptors in 1999. This nomenclature system was quickly accepted and has helped establish a standard chemokine terminology that has greatly facilitated their study. However, because of the rapid and divergent evolution of the chemokine system, species like humans and mice exhibit differences in their chemokine ligands (Zlotnik et al., 2006). The originally described chemokine relationships between human and mouse were based on sequence similarities and phylogenetic analyses. Consequently, there were some ambiguities in the assignment of species counterparts. We now have more powerful tools, including the human and mouse genomes, to improve on these analyses. The genomic organization of the human and mouse chemokine genes provides insights into the evolutionary forces that shape this superfamily and also confirm that in some cases, a given ligand exists in one species but not the other (Nomiya et al., 2010; Zlotnik et al., 2006). Given these advances, we need to update the human and mouse chemokine nomenclature systems.



**Figure 1. Chromosomal Map of the Human Chemokine and Chemokine Receptor Genes**

The full set of human chromosomes is shown with the locations of the chemokine (white) and chemokine receptor (gray) genes indicated as follows.

into four subfamilies: CXC, CC, (X)C, and CX3C. In the CXC chemokines, one amino acid separates the first two cysteines, whereas in CC chemokines, these two cysteines are adjacent. A single member of the CX3C subfamily, CX3CL1 or fractalkine, has three amino acids between the two cysteines, whereas the first and third cysteines are missing in the (X)C subfamily. Recently, another possible type of chemokine (CX) has been reported in zebrafish (Nomiya et al., 2008), which lack one of the two N terminus cysteines but retain the third and fourth ones; however, there is no evidence that this latter kind of chemokine exists in mammals.

Besides the structural criteria, chemokines may be categorized into several functional groups (Moser et al., 2004). Inflammatory chemokines (termed “I” in Table 1) are those upregulated under inflammatory conditions and are mainly involved in the recruitment of leukocytes to inflamed tissues. Among them, CXC chemokines with an ELR (Glu-Leu-Arg) motif just prior to the first cysteine residue are angiogenic, a property probably mediated via the chemokine receptors CXCR1 and CXCR2, whereas the ligands CXCL4, CXCL9, CXCL10, and CXCL11 are non-ELR motif angiostatic chemokines (Kiefer and Siekmann, 2011). Homeostatic chemokines (termed “H” in Table 1) are those expressed constitutively in lymphoid or other organs and normally mediate homeostatic migration and homing of various cells (including lymphocytes). Some chemokines overlap both fields and are called dual-function chemokines (termed “D” in Table 1).

These classifications are at best operational and not mutually exclusive. Thus, some inflammatory chemokines may have homeostatic functions, whereas some homeostatic chemokines may be upregulated under certain “emergency” conditions.

Some chemokines, such as CCL14 and CCL15, are present at high concentrations in serum, have an extended N terminus, and are converted to high-affinity ligands by N-terminal cleavage. CCL23 also has a long N terminus, is closely related to CCL15,

Since 2000 (Zlotnik and Yoshie, 2000), in-depth analyses of the mouse and human genomes have identified all the chemokine genes. Table 1 contains the complete families of human and mouse chemokines. The chemokine molecular signature includes four conserved cysteine residues that form two disulfide bonds pairing the first with the third and the second with the fourth cysteines. Based on the arrangement of the N-terminal two cysteine residues, chemokines are grouped

and, along with them, is likely to form a subgroup of inflammatory chemokines termed plasma chemokines ("P" for plasma or precursor in Table 1) (Nomiya et al., 2010). Yet another group of chemokines represented by CXCL4, CXCL4L1, CXCL7, and CCL5 are stored at high concentrations in  $\alpha$ -granules of platelets and quickly released upon platelet activation (Flad and Brandt, 2010). They probably have important roles as first-line inflammatory mediators upon vascular injury. One of these, CXCL4 (PF4), is one of the oldest members of the chemokine superfamily. However, its biological significance is still obscure. Although CXCR3-B (a CXCR3 splice variant) is believed to mediate the angiostatic activity of CXCL4 and other non-ELR CXC chemokines (CXCL9, CXCL10, CXCL11) (Lasagni et al., 2003), the mechanism remains unknown. CXCL4L1 is the nonallelic variant of CXCL4, differs from CXCL4 by only three amino acids within the C terminus, and is more angiostatic than CXCL4 (Struyf et al., 2004). CCL5 is one of the most versatile chemokines, acting on as many as three chemokine receptors (CCR1, CCR3, and CCR5), and is highly inducible in many cells. Furthermore, it is abundantly stored in  $\alpha$ -granules of platelets and in cytoplasmic granules of memory or effector CD8<sup>+</sup> T cells as well (Catalfamo et al., 2004). Functionally, CXCL4 and CCL5 appear to be closely associated, possibly through the formation of heteroligomers. CXCL7 is stored in inactive form and upon release is progressively processed at the N terminus by neutrophil cathepsin G from platelet basic protein (PBP) (aa 35–128) to connective tissue activating peptide (CTAP-III) (aa 44–128), to beta thromboglobulin ( $\beta$ -TG) (aa 48–128), and finally to neutrophil activating peptide (NAP-2) (aa 59–128), a high-affinity CXCR2 ligand. Thus, neutrophil attraction and proteolytic activation of CXCL7 form an amplification loop. Meanwhile, PBP and its processed products, along with CXCL4, have potent antimicrobial activities and are also called thrombocidins. Collectively, these chemokines are often termed platelet chemokines (termed "Pt" for platelet in Table 1) (Flad and Brandt, 2010).

The differences between inflammatory and homeostatic chemokines have an evolutionary origin, and it centers on the rapid evolution of the former (Nomiya et al., 2010). Inflammatory chemokines are clustered in chromosome 4 and chromosome 17 in the human (Figure 1). The reason for such rapid evolution in inflammatory chemokines is not clear but probably is a result of strong selective pressure to increase their members when early humans (or mice) faced a new pathogen that represented a serious threat to their survival. Furthermore, individual inflammatory chemokines can also differ markedly in their function between species (Islam et al., 2011). Finally, many inflammatory chemokines exist only in mouse or human (for example, CXCL8, Cxcl15, etc.) (see Table 1); this is probably the result of different pathogen-driven evolutionary experiences of the mouse and human lineages. We should note that the original nomenclature was aimed at the human chemokines, designated in capital letters; the mouse chemokines are designated in lower-case letters (Table 1).

The rapid evolution of inflammatory chemokines often makes the orthologous relationships obscure by phylogenetic analysis, even between human and mouse (Nomiya et al., 2010). For example, the three human paralogs CXCL1, CXCL2, and CXCL3 are structurally similar, and the same applies to their mouse counterparts (Nomiya et al., 2010). It is therefore

impossible to determine their orthologous relationships just from phylogenetic analyses. In such cases, analysis of the syntenic regions between the two genomes can be used to correctly assign species counterparts. The latter approach reveals that the mouse orthologs of human CXCL6, CXCL4L1, CXCL1, and CXCL3 correspond to *Cxcl5*, *Cxcl4*, *Cxcl3*, and *Cxcl1*, respectively (Nomiya et al., 2010). Indeed, mouse *Cxcl5* is closer to human CXCL6 than to CXCL5, and recently the rat gene symbol *Cxcl5* has been renamed *Cxcl6* (Nomiya et al., 2010). Similar analyses in the CC chemokines indicate that the mouse homologs of human CCL15 and CCL23 are *Ccl9* and *Ccl6*, respectively (Nomiya et al., 2010).

Islam et al. (2011) have shown that, although mouse Ccl8 is considered a member of the MCP (monocyte chemotactic protein) subfamily, it does not signal via Ccr2 but is instead a potent agonist for Ccr8, until now considered the sole receptor for Ccl1. However, human CCL8 is not a CCR8 agonist. These divergent results may be explained by the fact that mouse Ccl8 is actually not the counterpart of human CCL8 but is instead a mouse-specific chemokine like mouse Ccl12 (Table 1). Conversely, human CCL13 has no mouse counterpart. The chromosomal gene order of the human MCP-1 locus is CCL2-CCL7-CCL11-CCL8-CCL13-CCL1 (note fourth and fifth genes), whereas in the mouse it is *Ccl2-Ccl7-Ccl11-Ccl12-Ccl8-Ccl1* (different fourth and fifth genes) (Nomiya et al., 2010). Thus, the correct relationships, if any, of these genetically related chemokines still need to be determined. The importance of these observations is obvious when studying the effects of these chemokines in mouse models and their relevance to human disease.

In contrast, homeostatic chemokines are located singly or in miniclusters in different chromosomes (Figure 1). They are relatively ancient in evolutionary terms, well conserved between species, and function in a more predictable manner. For these reasons, the conclusions of studies in genetically modified mice deficient in homeostatic chemokines are more likely to apply to human physiology.

### Chemokine Receptors

Chemokine receptors are class A GPCRs coupled with the *G $\alpha$ i* class of the heterotrimeric G proteins. They are also grouped into four subfamilies according to the subfamily of their major chemokine ligands (Zlotnik et al., 2006). Like the ligand counterpart genes, the chemokine receptor genes also form clusters. A large cluster is located in human chromosome 3 (Figure 1), suggesting a rapid evolution through repeated gene duplications. However, compared to the ligands, chemokine receptors are relatively well conserved between species (including human and mouse) (Nomiya et al., 2011). Table 2 summarizes all known chemokine receptors. So far, 18 chemokine receptors with the standard *G $\alpha$ i*-dependent chemotactic activity have been identified in human and mouse. Furthermore, five atypical (nonchemotactic, recycling, or scavenging) chemokine receptors have been described. It is apparent that the chemokine receptors of inflammatory chemokines tend to have large numbers of chemokine ligands, and some ligands are also shared by multiple receptors (Nomiya et al., 2011).

In another twist, some chemokines can also function as natural chemokine antagonists of other ligand-receptor pairs

**Table 1. Human and Mouse Chemokines**

Chemokine	Other Names (Human)	Category	Gene Symbol		Other Names (Mouse)	Receptor	
			Human	Mouse <sup>a</sup>		Agonistic	Antagonistic
CXC Subfamily							
CXCL1	GRO $\alpha$ , MGSA	I, ELR	<i>CXCL1</i>	<i>Cxcl3</i> <sup>b</sup>	Gm1960	CXCR2	
CXCL2	GRO $\beta$	I, ELR	<i>CXCL2</i>	<i>Cxcl2</i>	MIP-2	CXCR2	
CXCL3	GRO $\gamma$	I, ELR	<i>CXCL3</i>	<i>Cxcl1</i> <sup>b</sup>	KC	CXCR2	
CXCL4	PF4	Pt, non-ELR	<i>PF4</i>	–		CXCR3-B	
CXCL4L1	PF4V1	Pt, non-ELR	<i>PF4V1</i>	<i>Pf4</i> <sup>b</sup>		CXCR3-B	
CXCL5	ENA78	I, ELR	<i>CXCL5</i>	–		CXCR2	
CXCL6	GCP2	I, ELR	<i>CXCL6</i>	<i>Cxcl5</i> <sup>b</sup>	LIX	CXCR1, CXCR2	
CXCL7	NAP-2	Pt, I, ELR	<i>PPBP</i>	<i>Ppbp</i>		CXCR1, CXCR2	
CXCL8	IL-8	I, ELR	<i>IL-8</i>	–		CXCR1, CXCR2	
CXCL9	MIG	I, non-ELR	<i>CXCL9</i>	<i>Cxcl9</i>		CXCR3	CCR3
CXCL10	IP-10	I, non-ELR	<i>CXCL10</i>	<i>Cxcl10</i>		CXCR3	CCR3
CXCL11	I-TAC	I, non-ELR	<i>CXCL11</i>	<i>Cxcl11</i>		CXCR3, CXCR7	CCR3, CCR5
CXCL12	SDF-1	H, non-ELR	<i>CXCL12</i>	<i>Cxcl12</i>		CXCR4, CXCR7	
CXCL13	BLC, BCA-1	H, non-ELR	<i>CXCL13</i>	<i>Cxcl13</i>		CXCR5, CXCR3	
CXCL14	BRAK	H, non-ELR	<i>CXCL14</i>	<i>Cxcl14</i>		unknown	
–	–	U, non-ELR	–	<i>Cxcl15</i>	Lungkine, Weche	unknown	
CXCL16	SR-PSOX	I	<i>CXCL16</i>	<i>Cxcl16</i>		CXCR6	
CXCL17	DMC	U	<i>CXCL17</i>	<i>Cxcl17</i>		unknown	
CC Subfamily							
CCL1	I-309	I	<i>CCL1</i>	<i>Ccl1</i>	TCA-3	CCR8	
CCL2	MCP-1	I	<i>CCL2</i>	<i>Ccl2</i>	JE	CCR2	
CCL3	MIP-1 $\alpha$ , LD78 $\alpha$	I	<i>CCL3</i>	<i>Ccl3</i>		CCR1, CCR5	
CCL3L1	LD78 $\beta$	I	<i>CCL3L1</i>	–		CCR1, CCR3, CCR5	
CCL3L3	LD78 $\beta$	I	<i>CCL3L3</i>	–			
CCL4	MIP-1 $\beta$	I	<i>CCL4</i>	<i>Ccl4</i>		CCR5	
CCL4L1	AT744.2	I	<i>CCL4L1</i>	–			
CCL4L2	–	I	<i>CCL4L2</i>	–			
CCL5	RANTES	I, Pt	<i>CCL5</i>		Ccl5	CCR1, CCR3, CCR5	
CCL7	MCP-3	I	<i>CCL7</i>	<i>Ccl7</i>	MARC	CCR1, CCR2, CCR3	CCR5
CCL8	MCP-2	I	<i>CCL8</i>	–		CCR1, CCR2, CCR5	
–	–	I		<i>Ccl8</i> <sup>b</sup>		CCR8 (mouse)	
CCL11	Eotaxin	D	<i>CCL11</i>	<i>Ccl11</i>		CCR3, CCR5	CXCR3, CCR2
–	–	I	–	<i>Ccl12</i>	MCP-5		
CCL13	MCP-4	I	<i>CCL13</i>	–		CCR2, CCR3	
CCL14	HCC-1	P	<i>CCL14</i>	–		CCR1, CCR3, CCR5	
CCL15	HCC-2, Leukotactin-1	P	<i>CCL15</i>	<i>Ccl9</i> <sup>b</sup>	CCF18, MIP-1 $\gamma$	CCR1, CCR3	
CCL16	LEC, HCC-4	U	<i>CCL16</i>	–		CCR1, CCR2, CCR5, CCR8, H4	
CCL17	TARC	D	<i>CCL17</i>	<i>Ccl17</i>	ABCD-2	CCR4	
CCL18	PARC, DC-CK1	H	<i>CCL18</i>	–		PITPNM3	CCR3
CCL19	MIP-3 $\beta$ , ELC	H	<i>CCL19</i>	<i>Ccl19</i>		CCR7	
CCL20	MIP-3 $\alpha$ , LARC	D	<i>CCL20</i>	<i>Ccl20</i>		CCR6	
CCL21	SLC, 6Ckine	H	<i>CCL21</i>	<i>Ccl21a</i>		CCR7	CXCR3 (mouse)
–	–	H	–	<i>Ccl21b</i>		CCR7	
–	–	H	–	<i>Ccl21c</i>		CCR7	
CCL22	MDC	D	<i>CCL22</i>	<i>Ccl22</i>	ABCD-1	CCR4	

**Table 1. Continued**

Chemokine	Other Names (Human)	Category	Gene Symbol		Other Names (Mouse)	Receptor	
			Human	Mouse <sup>a</sup>		Agonistic	Antagonistic
CCL23	MPIF-1	P	<i>CCL23</i>	<i>Ccl6<sup>b</sup></i>	C10	CCR1, FPRL-1	
CCL24	Eotaxin-2, MPIF-2	H	<i>CCL24</i>	<i>Ccl24</i>		CCR3	
CCL25	TECK	H	<i>CCL25</i>	<i>Ccl25</i>		CCR9	
CCL26	Eotaxin-3	I	<i>CCL26</i>	( <i>Ccl26</i> )		CCR3, CX3CR1	CCR1, CCR2, CCR5
CCL27	CTACK, ILC	H	<i>CCL27</i>	<i>Ccl27a</i>		CCR10	
-	-	H	-	<i>Ccl27b</i>			
CCL28	MEC	H	<i>CCL28</i>	<i>Ccl28</i>		CCR10, CCR3	
XC Subfamily							
XCL1	Lymphotactin, ATAC, SCM-1 $\alpha$	D	<i>XCL1</i>	<i>Xcl1</i>	lymphotactin	XCR1	
XCL2	SCM-1 $\beta$	D	<i>XCL2</i>	-		XCR1	
CX3C Subfamily							
CX3CL1	Fractalkine	D	<i>CX3CL1</i>	<i>Cx3cl1</i>	fractalkine, neurotactin	CX3CR1	

Abbreviations: I, inflammatory chemokines; H, homeostatic chemokines; D, dual chemokines; P, plasma or platelet chemokines that are activated by cleavage; Pt, platelet chemokines; U, unknown. Mouse genes whose human counterparts are reassigned by synteny analysis are highlighted by underline. H4, histamine receptor type 4; PITPNM3, phosphatidylinositol transfer protein membrane associated 3; FPRL-1, formyl peptide receptor like-1.

<sup>a</sup>Genes appearing in parentheses are not expressed.

<sup>b</sup>Mouse gene whose human counterpart was reassigned after syntenic analysis.

(Table 2). For example, ligands of CXCR3 and CCR3 are reciprocally natural antagonists (Loetscher et al., 2001; Weng et al., 1998). Thus, CXCL9, CXCL10, and CXCL11 are natural antagonists for CCR3, whereas CCL11 is a natural antagonist for CXCR3. Given that CXCR3 is a T helper 1 (Th1) cell-associated chemokine receptor, whereas CCR3 is expressed by Th2 cells and eosinophils, this suggests that these chemokines can form mutually exclusive microenvironments that favor either Th1 or Th2 cell differentiation (Sallusto and Lanzavecchia, 2000).

Nonchemokine ligands can also bind certain chemokine receptors. Though still controversial, *N*-acetyl Pro-Gly-Pro (acPGP), a neutrophil protease-mediated degradation product of extracellular matrix, can be a Cxcr1 and Cxcr2 agonist (Weathington et al., 2006). Thus, production of this tripeptide by infiltrating neutrophils may recruit yet more neutrophils via Cxcr1 and Cxcr2. Macrophage migration inhibitory factor (MIF) is an evolutionary conserved cytokine with proinflammatory functions and has also been claimed to be a noncanonical CXCR2 and CXCR4 ligand (Bernhagen et al., 2007). Extracellular ubiquitin, which has anti-inflammatory properties, is another nonchemokine CXCR4 ligand (Saini et al., 2010). Finally, the nuclear protein HMGB1 can also interact with CXCL12 and mediates mononuclear cell recruitment in vivo via CXCR4 (Schiraldi et al., 2012).

Antimicrobial peptides are natural antibiotics of multicellular organisms and often exhibit chemotactic activity.  $\beta$ -defensins are antimicrobial peptides expressed by epithelial cells of the body surface (Ouellette, 2011). Like CCL20,  $\beta$ -defensin-2 attracts immature dendritic and memory T cells via CCR6 (Yang et al., 1999).  $\beta$ -defensins 2 and 3 also function as noncanonical ligands for CCR2 (Röhrli et al., 2010). Conversely,

a growing number of chemokines mediate direct antimicrobial activities (Eliasson and Egesten, 2008). It is therefore possible that chemokines and antimicrobial peptides share a common evolutionary origin. Alternatively, the selective pressures exerted by the pathogens on their hosts may have led the chemokines and antimicrobial peptides to perform overlapping functions.

In contrast to inflammatory chemokine receptors, homeostatic or dual-function chemokine receptors show more restricted ligand usages: just one or two ligands (Table 2). Furthermore, even in the case of two ligands, most are not just redundant but appear instead to have specific roles. For example, CCR4, which is expressed by Th2 cells, skin-homing T cells, and regulatory T cells, has two ligands: CCL17 and CCL22. In inflamed skin tissues, CCL17 is expressed by skin microvascular endothelial cells, whereas CCL22 is expressed by dermal dendritic cells. Thus, CCR4-expressing T cells are first exposed to CCL17 on skin endothelial cells and then guided into skin tissues by CCL22 (Mariani et al., 2004). This sequential interaction of ligands seems to be possible because CCL17 does not induce desensitization of CCR4, whereas CCL22, being a stronger ligand for CCR4, can override the prior effect of CCL17 to guide T cells away from CCL17 (Mariani et al., 2004). Another example is CCR7 and its two ligands, CCL19 and CCL21, which play an essential role in the homing of lymphocytes and dendritic cells to secondary lymphoid tissues. Although both CCL19 and CCL21 are coexpressed in the T cell zone of secondary lymphoid tissues, only CCL21 is expressed or presented by high endothelial venules (HEV). Similarly, only CCL21 is expressed on afferent lymphatic vessels. CCL21 but not CCL19 can also be immobilized to the cell surface through its highly charged 40 amino acid extension at the C terminus. On the other hand, only



**Table 2. Human and Mouse Chemokine Receptors**

Human Gene Symbol	Other Names	Category	Mouse Gene Symbol	Ligands	
				Agonistic	Antagonistic
CXCR Subfamily					
CXCR1	IL-8RA	I	Cxcr1	CXCL6, CXCL7, CXCL8, acPGP	
CXCR2	IL-8RB	I	Cxcr2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8, acPGP, MIF	
CXCR3	GPR9	I	Cxcr3	CXCL4 (CXCR3-B), CXCL9, CXCL10, CXCL11, CXCL13, CCL21 (mouse)	CCL11
CXCR4	LESTER, Fusin	H	Cxcr4	CXCL12, MIF, ubiquitin	
CXCR5	BLR1	H	Cxcr5	CXCL13	
CXCR6	STRL33, BONZO	H	Cxcr6	CXCL16	
CCR Subfamily					
CCR1	CC-CKR-1	I	Ccr1	CCL3, CCL3L1, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL16, CCL23	CCL26
CCR2	CC-CKR-2	I	Ccr2	CCL2, CCL7, CCL8, CCL13, CCL16, $\beta$ -defensin 2,3	CCL11, CCL26
CCR3	CC-CKR-3	I	Ccr3	CCL3L1, CCL5, CCL7, CCL11, CCL13, CCL14, CCL15, CCL24, CCL26, CCL28	CXCL9, CXCL10, CXCL11, CCL18
CCR4	CC-CKR-4	D	Ccr4	CCL17, CCL22	
CCR5	CC-CKR-5	I	Ccr5	CCL3, CCL3L1, CCL4, CCL4L1, CCL5, CCL8, CCL11, CCL16	CCL7, CXCL11, CCL26
CCR6	STRL22, GPR29	I	Ccr6	CCL20, $\beta$ -defensin-2	
CCR7	EBI1, BLR2	H	Ccr7	CCL19, CCL21	
CCR8	TER1, GPR-CY6	H	Ccr8	CCL1, CCL8 (mouse)	
CCR9	GPR-9-6	H	Ccr9	CCL25	
CCR10	GPR2	H	Ccr10	CCL27, CCL28	
XCR Subfamily					
XCR1	GPR-5	D	Xcr1	XCL1, XCL2	
CX3CR Subfamily					
CX3CR1	V28, GPR13	D	Cx3cr1	CX3CL1, CCL26 (human)	
Atypical (Nonchemotactic, Recycling or Scavenger Receptors)					
CXCR7	RDC1, GPR159		Cxcr7	CXCL11, CXCL12	
CCBP2	D6		Ccbp2	CCL2, CCL3, CCL3L1, CCL4, CCL4L1, CCL5, CCL7, CCL8, CCL11, CCL12, CCL13, CCL14, CCL17, CCL22, CCL23, CCL24	
CCRL1	CCX-CKR		Ccrl1	CCL19, CCL21, CCL25, CXCL13	
CCRL2	HCR, CRAM		Ccrl2	CCL19, chemerin	
DARC	Duffy		Darc	CXCL1, CXCL2, CXCL3, CXCL7, CXCL8, CCL2, CCL5, CCL11, CCL13, CCL14, CCL17	

Abbreviations: acPGP, *N*-acetyl Pro-Gly-Pro; MIF, macrophage migration inhibitory factor.

CCL19 but not CCL21 can desensitize and internalize CCR7 (Nandagopal et al., 2011; Schumann et al., 2010). Thus, the likely scenario is that CCL21 guides lymphocytes and dendritic cells expressing CCR7 into lymph nodes and T cell zones via HEVs and afferent lymphatics. Then, CCL19 overrides CCL21-mediated migration and desensitizes CCR7. Downregulation of CCR7 is also necessary for B and follicular helper T cells expressing CXCR5 to redirect their migration to the B cell zone via CXCL13 expressed by follicular dendritic cells (Haynes et al., 2007). These examples illustrate how a set of a single receptor with a pair of chemokines can play a combinatorial or functionally differential role in target cell migration.

### Atypical Chemokine Receptors

There are also five atypical chemokine receptors (Table 2). They can bind a large number of chemokine ligands. Recently, atypical or decoy chemokine receptors have attracted attention because of their influence on the availability and function of both inflammatory and homeostatic chemokines. They are not just chemokine binding proteins, but standard heptahelical membrane-spanning receptors similar to classical chemokine receptors. Still, they do not transduce the full spectrum of chemokine receptor signals that lead to chemotactic and other cellular responses. This is partly because of either modification or lack of the typical DRY motif in the second intracellular loop

(DRLAIV) known to be important for efficient coupling with the G $\alpha$ i class G-proteins. Their functions include either chemokine scavenger or decoy (interceptor) receptors or transporters. There are excellent reviews on this subject (Mantovani et al., 2006; Ulvmar et al., 2011). In brief, DARC (duffy antigen chemokine receptor) is the classic example of an atypical chemokine receptor. DARC binds a large number of CXC and CC inflammatory but not homeostatic chemokines, is abundantly expressed by erythrocytes, and functions as a chemokine sink. DARC is also expressed by venular endothelial cells and mediates chemokine transcytosis from the basolateral to the apical side. This may promote leukocyte emigration at inflammation sites (Pruenster and Rot, 2006). CCR2 (D6) is another atypical chemokine receptor binding a large number of inflammatory CC chemokines. Given that D6 is expressed by the endothelial cells of afferent lymphatic vessels, its main role may be scavenging chemokines in the lymphatic flow to prevent leukocyte activation within the lymphatics. Indeed, *Ccr2*<sup>-/-</sup> mice exhibited increased inflammatory responses in D6-expressing tissues such as skin, placenta, lung, etc., when challenged with various stimuli (Graham, 2009). CXCR7 is an interesting atypical chemokine receptor (Maksym et al., 2009). Together with CXCR4 and its ligand CXCL12, CXCR7 is conserved well across the vertebrate species including sea lamprey (Nomiya et al., 2011). It binds CXCL11 and CXCL12. Importantly, CXCR7 can heterodimerize with CXCR4 and modulate the effect of CXCL12 on CXCR4. Furthermore, CXCR7 can also signal in some cell types although not by the classical G protein-coupled receptor pathways (Maksym et al., 2009). During embryogenesis, CXCR7 is necessary for proper migration of primordial germ cells to CXCL12 via CXCR4 by acting as a sink for CXCL12 (Boldajipour et al., 2008). CXCR7 is also involved in cardiac tissue development along with CXCR4 and CXCL12 (Sierro et al., 2007). Although poorly expressed in normal adult tissues, CXCR7 is widely expressed in a variety of tumors and tumor-associated vessels and appears to promote tumor growth and neoangiogenesis partly by signaling via mitogen activated protein kinase (MAPK) cascades (Maksym et al., 2009). CCRL1 and CCRL2 differ from other atypical receptors in their ability to bind and scavenge homeostatic chemokines, particularly the CCR7 axis (Comerford et al., 2006; Leick et al., 2010). Thus, they are considered to play a regulatory role in the homeostatic migration of lymphocytes and dendritic cells via CCR7. Interestingly, chemerin, a chemoattractant for myeloid-lineage cells including myeloid and plasmacytoid dendritic cells and potential adipokine signaling via ChemR23, also binds CCRL2 without signaling (Bondue et al., 2011). CCRL2 has been shown to play an important role in lung DC trafficking (Otero et al., 2010).

## Chemokines and the Immune System

### T Cell Plasticity

Chemokine receptors have been associated with specific polarized subsets of CD4<sup>+</sup> T cells that participate in various immune responses. Th1 cells express CCR5 and CXCR3, whereas Th2 cells express CCR4 (Sallusto and Lanzavecchia, 2000) and CCR8 (Zingoni et al., 1998). Th17 cells express CCR6 (Singh et al., 2008) and this is likely to be the signal that recruits these cells to the small intestine when it becomes colonized by the microbiome (Esplugues et al., 2011), whereas T regulatory

(Treg) cells express CCR4 (Hirahara et al., 2006) and also CCR6 (Kitamura et al., 2010). These observations indicate that different chemokine ligands, probably produced by antigen-presenting or immunomodulatory cells, have the capacity to direct the migration of these different subsets within the body (Sallusto and Baggiolini, 2008). Chemokines can also influence macrophage plasticity and their interaction with lymphocytes (Biswas and Mantovani, 2010).

### Skin Chemokines

Several chemokines have evolved to be present in these tissues. The most skin-associated chemokine is CCL27. Other chemokines expressed in the skin include CXCL14 and several inflammatory chemokines that are expressed in the skin under inflammatory conditions. The roles of CCL17 and CCL22 as well as their receptor CCR4 in the skin were discussed above.

CCL27 was originally called CTACK for cutaneous T cell attracting chemokine (Morales et al., 1999). It is specifically and strongly expressed in the skin by keratinocytes. CCL27 binds CCR10 (GPR2), a class A GPCR (Wang et al., 2000). CCR10 is not widely expressed as other chemokine receptors; instead, in the skin it is expressed strongly by melanocytes (and also by melanoma cells). This skin expression pattern suggests that the CCL27-CCR10 axis participates in skin development, although a *Ccr10*<sup>-/-</sup> mouse does not exhibit skin abnormalities (Morteau et al., 2008). A well-documented function of the CCL27-CCR10 axis in the skin is the recruitment of a subset of T cells to the skin that express cutaneous lymphocyte antigen (CLA) (Morales et al., 1999). The function of these skin-specific T cells remains obscure, but they are believed to represent memory cells that participate in local responses (Clark et al., 2006).

CXCL14 is a very interesting chemokine. It was originally reported as BRAK (breast and kidney chemokine) because of its high expression in these tissues (Hromas et al., 1999). It is, along with CXCL12, one of the most conserved chemokines (Zlotnik et al., 2006), suggesting that it has important evolutionary functions. It exhibits microbicidal activity (Maerki et al., 2009), suggesting that this may be its main role in the skin.

### Mucosal Chemokines

Two chemokines are well known as mucosal chemokines (CCL25 and CCL28) and two other chemokines (CXCL14 and CXCL17) are also expressed in the mucosa but are not widely known as mucosal chemokines. CCL25 was originally reported as TECK (thymus-expressed chemokine) because it was originally isolated from the thymus where it exhibits very strong expression (Vicari et al., 1997) and participates in T cell development (see below). The only other site where it is strongly expressed is the small intestine (Vicari et al., 1997). Its receptor is CCR9, another class A GPCR that does not exhibit a wide expression pattern (Norment et al., 2000). Like the CCL27-CCR10 axis, the CCL25-CCR9 axis is responsible for recruiting a certain subset of T cells to the lamina propria of the intestine (Kunkel et al., 2000) that express both CCR9 and  $\alpha$ 4 $\beta$ 7 integrin (Papadakis et al., 2000). These cells have become important because they are involved in the pathogenesis of Crohn's disease and ulcerative colitis. In fact, several companies have been developing CCL25-CCR9 axis inhibitors and some of these are in clinical trials in Crohn's disease (Eksteen and Adams, 2010).

Another interesting aspect of the CCL25-CCR9 axis is the expression of CCR9 in a subset of melanomas (Amersi et al., 2008). The expression of certain homeostatic chemokine receptors in tumor cells influences their metastatic potential (Zlotnik et al., 2011). If tumor cells of a certain cancer express a given homeostatic chemokine receptor, they may preferentially metastasize to organs where the ligand of that receptor is expressed. Melanoma does not usually metastasize to the small intestine; however, if melanoma tumor cells express CCR9, then intestinal metastases are observed (Amersi et al., 2008).

CCL28 was originally identified as a product of epithelial cells and also binds CCR10 (Wang et al., 2000). It is one of the most mucosal-associated chemokines. It is highly expressed in the salivary gland, the female reproductive tissues, and the mammary gland (Bourges et al., 2008). It is detectable in saliva and exhibits microbicidal activity (Hieshima et al., 2003). Interestingly, its expression in the mammary gland is induced upon the onset of lactation (Wilson and Butcher, 2004). CCL28 attracts plasmablasts that produce IgA through CCR10 (Kunkel et al., 2003) and is responsible for the production of IgA in certain mucosal sites (Hieshima et al., 2004; Morteau et al., 2008). A *Ccr10*<sup>-/-</sup> mouse exhibits defective IgA responses in the mammary gland (Morteau et al., 2008).

Less is known about the other two mucosal chemokines, CXCL14 and CXCL17. CXCL14 is expressed in several mucosal sites (Meuter and Moser, 2008; Shellenberger et al., 2004). In some sites, CXCL14 can exhibit surprising expression specificity. For example, in the tongue, CXCL14 is strongly expressed in the taste buds but not in lingual epithelium (Hevezi et al., 2009), although its function there is currently unknown. CXCL14 is also expressed in the intestines, and a *Cxcl14*<sup>-/-</sup> mouse shows metabolic abnormalities (Nara et al., 2007) and also grows at a slower rate (Tang et al., 2010). Because CXCL14 is a strongly conserved chemokine, it is possible that these defects reflect developmental abnormalities. Importantly, its receptor has not been identified yet.

CXCL17 was the last chemokine to be reported and characterized (Pisabarro et al., 2006) and there is little information about it in the literature. Originally reported as DMC (dendritic cell and macrophage chemokine), it is the last human chemokine ligand of the CXCL family. It is expressed in stomach and trachea (Pisabarro et al., 2006). It has recently been confirmed to be a mucosal chemokine because its expression is restricted to bronchus and trachea, tongue, oral cavity, stomach, small intestine, and colon and it exhibits microbicidal activity (A.M. Burkhardt, K.I. Tai, J.P. Flores-Gutierrez, M. Vilches-Cisneros, K. Kamdar, O. Barbosa-Quintana, R. Valle-Rios, P.A. Hevezi, A.J. Ouellette, and A.Z., in press). In contrast to CXCL14 that in the tongue is expressed in the taste buds, CXCL17 is expressed in the lingual epithelium but not in the taste buds (A.M. Burkhardt, K.I. Tai, J.P. Flores-Gutierrez, M. Vilches-Cisneros, K. Kamdar, O. Barbosa-Quintana, R. Valle-Rios, P.A. Hevezi, A.J. Ouellette, and A.Z., unpublished data). This is an example of highly specific expression patterns that chemokines can have in the mucosa, although its functional significance is currently unknown. It attracts dendritic cells and monocytes (Pisabarro et al., 2006) and is induced by VEGF (vascular endothelial growth factor) (Weinstein et al., 2006). Like CXCL14, its receptor is currently unknown.

### Chemokines in T Cell Development

Several chemokines are highly expressed in sites of lymphoid development like the thymus, bone marrow, or fetal liver. There are specific examples of chemokines important in lymphoid development. One of these is the CCL25-CCR9 axis, which plays an important role in T cell development in the thymus (Vicari et al., 1997).

T cell development in the thymus commences when hematopoietic precursors from the bone marrow colonize the thymus. Some chemokines participate in the seeding of the thymus rudiment by hematopoietic bone marrow precursors. *Ccr7*<sup>-/-</sup> and *Ccr9*<sup>-/-</sup> mice were shown to exhibit defective thymus colonization (Krueger et al., 2010; Zlotoff et al., 2010). A more recent study used a triple-deficient mouse (CXCR4, CCR7, and CCR9) and observed a more profound defect (Calderón and Boehm, 2011), suggesting that several chemokines participate in this seeding process.

Once early T cell progenitors enter the thymus, they are CD4<sup>-</sup>CD8<sup>-</sup> (double-negative, DN) and are not yet committed to the T cell lineage (Godfrey and Zlotnik, 1993). These are called DN1. As they commit to the T cell lineage, they become DN2 and start to rearrange the  $\beta$  chain of the T cell receptor (TCR) (Godfrey et al., 1994) and subsequently become DN3. DN3 thymocytes that successfully rearrange the TCR $\beta$  chain in-frame express this chain with the pre-T alpha (Kometani et al., 2008) and undergo "beta selection," a step that allows the developing DN3 thymocytes to proceed become DN4. As a result of beta selection, DN3 thymocytes start to express CCR9 (Norment et al., 2000) and this allows them to become CD4<sup>+</sup>CD8<sup>+</sup> thymocytes. CCR9 is also required for progression from the CD4<sup>+</sup>CD8<sup>+</sup> stage to mature CD4<sup>+</sup> thymocytes (Svensson et al., 2008). Other chemokine receptors like CCR7 are also involved in T cell development in the thymus (Misslitz et al., 2006).

### Chemokines and Stem Cells

Hematopoietic stem cells (HSCs) are known to reside in the bone marrow. Broxmeyer et al. (2005) reported that the CXCR4 inhibitor AMD3100 induced release of HSCs from the bone marrow, indicating that the CXCR4-CXCL12 axis is a key signal maintaining HSCs in the bone marrow. This observation had potential clinical utility, because certain cancer patients are candidates for whole-body irradiation followed by reconstitution of the hematopoietic compartment via HSCs. Thus, the ability of the CXCR4 antagonist AMD3100 to release HSCs from the bone marrow meant that these "mobilized" HSCs could be isolated from the blood of the patient in sufficient numbers to permit repopulation with autologous HSCs (Uy et al., 2008). Interestingly, AMD3100 synergizes with granulocyte colony stimulating factor to mobilize HSCs, improving the effectiveness of the approach and allowing the isolation of enough cells for autologous cell transplantation. This combined approach has been used in patients with non-Hodgkin's lymphoma and with multiple myeloma (Pusic and DiPersio, 2010). Other CXCR4-based therapeutics have been reviewed recently (Peled et al., 2012).

These developments underscore the important roles that CXCR4 plays in development. Other studies have documented that the CXCL12-CXCR4 axis plays pivotal roles in homing of various stem cells to particular places of the embryo during



development. One of the most useful experimental models to understand these mechanisms has been the zebrafish, where CXCR4 is the signal that guides stem cells that give rise to the gonads of the developing fish embryo (Doitsidou et al., 2002; Knaut et al., 2003). More recent studies have documented the coordinated roles of CXCR4, CXCL12, and CXCR7 in the development of the central nervous system in the zebrafish (Diotel et al., 2010; Tiveron and Cremer, 2008). Thus, certain homeostatic chemokine receptors play key roles in the homing of various stem cells. The ability of the CXCR4-CXCL12 axis in directing stem cell homing is probably related to its prominent role in directing the metastatic destination of tumor cells as well (Zlotnik et al., 2011).

### Clinical Application of Chemokines

#### Chemokine Receptor Antagonists as Therapeutics

As discussed above, inflammatory chemokines are involved in control of inflammatory responses and several homeostatic chemokines are important in the control of immune responses, and their roles in development and cell migration also make them compelling targets for drug development. However, only recently have two drugs that target chemokine receptors been approved. One of these is a CCR5 antagonist that is approved for inhibition of entry of human immunodeficiency virus (HIV) into CCR5-positive cells (Gilliam et al., 2011). The other is a CXCR4 antagonist (AMD3100) that has been approved for mobilization of human hematopoietic stem cells from the bone marrow (Keating, 2011). The latter therapeutic use of a CXCR4 antagonist was predicted after the observation that blocking CXCR4 resulted in release of hematopoietic stem cells from the bone marrow (Broxmeyer et al., 2005). This approach is now used to obtain enough hematopoietic stem cells for use in autologous bone marrow transplants in patients with non-Hodgkin's lymphoma or multiple myeloma (Pusic and DiPersio, 2010).

Despite the predominant role that chemokines play in inflammatory responses, no chemokine-based drugs have been approved for autoimmune or inflammatory diseases. One possibility, as discussed above, is that animal models used for preclinical studies aimed to evaluate the role of inflammatory chemokines may not translate well for human diseases. Another possibility is that more focused targets will succeed in specific indications. For example, CCR9 antagonists are currently in clinical trials for inflammatory bowel diseases (Proudfoot et al., 2010), and CXCR3 antagonists (presumably because they target Th1 cell responses) also show promise in other indications (Liu et al., 2011). CCR4 may also be a target for adult T cell leukemia-lymphomas (Tobinai et al., 2012).

#### Can Chemokines Be Biomarkers?

Molecular characterization of various human diseases by gene arrays indicates that despite the complexity of this superfamily, chemokines usually exhibit remarkable specificity in their association with certain human diseases. This suggests another possible use of chemokines, namely, as potential biomarkers.

One example is hepatitis C, which is caused by the hepatitis C virus that infects the human liver. Until recently the treatment for chronic carriers was a combination therapy of interferon alpha (IFN- $\alpha$ ) and ribavirin, but 50% of the patients failed to clear the virus after this treatment (Tanaka et al., 2009). Infection with

the hepatitis C virus modulates the expression of many genes in the infected liver, including two chemokines, CXCL9 and CXCL10, which are strongly induced in the HCV-infected human liver (Hevezi et al., 2011). IL-28B is a cytokine that has been associated with the response to pegylated IFN- $\alpha$  and ribavirin in chronic hepatitis C patients (Ge et al., 2009; Tanaka et al., 2009). Darling et al. (2011) found that lower CXCL10 serum concentrations correlate with sustained virological response, whereas high pretreatment CXCL10 amounts in serum correlate with nonresponders. Thus, the combination of IL-28B single-nucleotide polymorphism (SNP) analyses along with CXCL10 serum concentrations may be effective predictors of response to treatment in hepatitis C patients (Albert et al., 2011).

Alterations in plasma CXCL10 concentrations have also been associated with onset of transplant rejection (Romagnani and Crescioli, 2012). Given that CXCL10 is a ligand of CXCR3 and the latter is associated with Th1 cell responses (Sallusto and Lanzavecchia, 2000), it is possible that serum CXCL10 concentrations may reflect Th1 cell response activity in vivo. High CXCL10 concentrations may also correlate with poor prognosis and metastasis in colorectal cancer (Toiyama et al., 2012). More information on this subject has been presented elsewhere (Amanatidou et al., 2011; Balkwill, 2012; Melve et al., 2011).

### Concluding Remarks

In order to understand the chemokine superfamily and its functions in the organism, it is better to study it from an evolutionary perspective. Whereas the function of inflammatory chemokines is more probably linked to resistance to infectious agents, homeostatic chemokines exhibit specific functions related to their expression site(s). Chemokines participate in the development of the immune system, in inflammatory responses, and in innate and acquired immune responses. The discoveries and accumulated knowledge in chemokine biology in the last 25 years have led to important advances in our understanding of immune responses and organization of the immune system. It is our hope that this review will help readers better understand the chemokine superfamily.

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