Chapter 1

The Chemokine Gene Family

Similar Structures, Diverse Functions

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1. Introduction

Our understanding of the function of chemokines has been reshaped over the past few years because of the large number of new chemokines recently discovered. Earlier reviews on chemokine structure and function presented a relatively simple picture of the chemokine family: a handful of CXC and CC chemokines, whose genes clustered on chromosomes 4 and 17, respectively, involved in the recruitment of leukocyte subsets to sites of inflammation *(1,2)*. Over the past few years, however, the use of computer technology to search vast libraries of randomly sequenced cDNAs has brought to light many novel chemokines that complicate the picture described above, but also enrich our understanding of the functional diversity of chemokines. Not only have new chemokine families and chromoobtained, and how they have broadened our understanding of the structure and function of chemokines.

2. Identification of New Chemokines

In the near future, the human genome will be entirely sequenced, enabling determination of the complete complexity of chemokine gene structures. According to current estimates, there may be as many as 50 chemokine genes encoded by the human genome. Meanwhile, largely as a result of cDNA sequencing efforts, the number of known chemokines has nearly doubled during the past few years. Some recently described chemokines include monocyte chemotactic peptide-4 (MCP-4) *(3)*, human CC chemokine-1 (HCC-1) *(4)*, HCC-2 (unpublished), liver and activation-regulated chemokine (LARC) *(5)*, pulmonary and activation-regulated chemokine (PARC) *(6)*, myeloid progenitor inhibitory factor-1 (MPIF-1) *(7)*, MPIF-2 *(7)*, thymus and activation-regulated chemokine (TARC) *(8)*, macrophage-derived chemokine (MDC) *(9)*, EBI ligand

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Table 1
Key to Chemokine Names

Chemokine	Also known as
ELC *(10)*	MIP-3β *(85)*
Fractalkine *(13)*	Neurotactin *(31)*
	NKAF *(84)*
HCC-1 *(4)*	NCC-2 *(28)*
LARC *(5)*	Exodus *(69)*
	MIP-3α *(85)*
Lymphotactin *(26)*	SCM-1 *(86)*
MCP-4 *(3,59,60)*	NCC-1 *(28)*
MDC *(9)*	STCP-1 *(87)*
MPIF-1 *(7)*	CKβ-8 *(7)*
	MIP-3 *(84)*
MPIF-2 *(7)*	CKβ-6 *(7)*
	Eotaxin-2 *(61,62)*
PARC *(6)*	DC-CK-1 *(88)*
	MIP-4 *(84)*
SLC *(11)*	Exodus-2 *(70)*
	6Ckine *(89)*

chemokine (ELC) *(10)*, secondary lymphoid-tissue chemokine (SLC) *(11)*, thymus-expressed chemokine (TECK) *(12)*, and fractalkine *(13)*. Many of these chemokines were identified using computer searches of sequence databases. Because of the speed and ease with which computer searches can be performed, most of these chemokines were identified by multiple groups and are therefore often known by several different names. For the purposes of this review, we will use the names above to refer to these new chemokines; however, Table 1 lists other authors who have described these chemokines and the names they have used.

To illustrate the frequency with which chemokines are represen-ted in the public domain database, the DNA sequence of each known chemokine was compared to the GenBank expressed sequence tag (EST) database using the BLASTYN program *(14)*. Figure 1 presents a bar graph indicating the number of EST "hits" found for each known chemokine. Interleukin 8 (IL-8) is by far the most highly represented chemokine with over 180 ESTs, about three times higher than the number of hits for the next most abundant family members. Care must be taken in drawing conclusions from this analysis, because mRNA abundance does not always correlate with protein expression and not all tissues are equally represented in the EST database. In addition, some of the cDNA libraries used for EST analysis have been normalized by a hybridization technique that increases the representation of rare transcripts *(15)*. Nevertheless, IL-8 appears to be a highly expressed chemokine found in many tissues and cell types. Of the CC chemokines, the most abundant ESTs are found for macrophage inflammatory protein-1α (MIP-1α), MIP-1β, and monocyte chemotactic peptide 1 (MCP-1). Some chemokines, such as granulocyte chemotactic protein-2 (GCP-2) and TARC, are not represented in the EST database, probably because libraries from appropriate tissues have not yet been sequenced. Chemokines with larger transcript sizes such as MDC *(9)* may go unnoticed in a search of the EST database. Such chemokines may nevertheless play critical physiological roles.

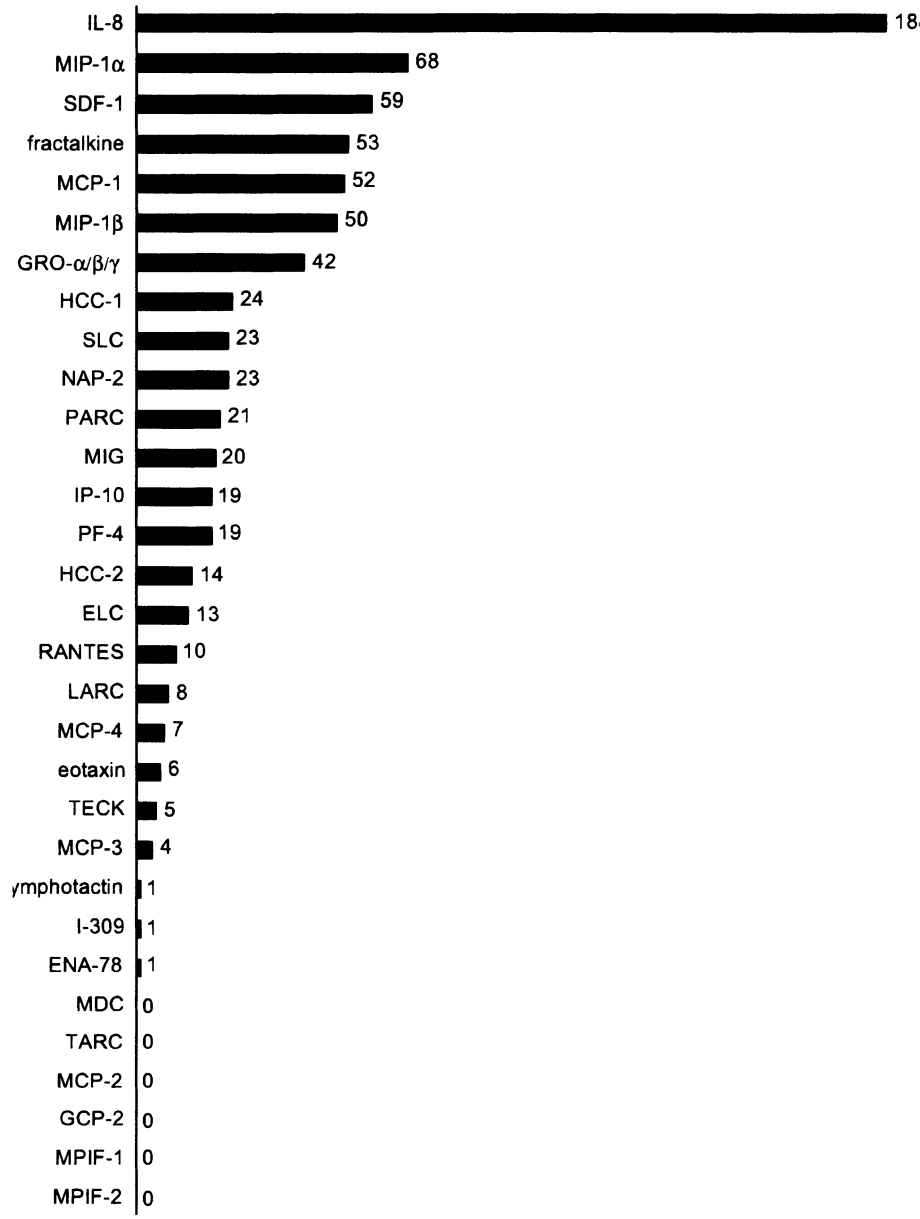

Fig. 1. Frequency of chemokine cDNAs in the GenBank EST database. The complete cDNA sequence for each chemokine was compared against dbEST using the BLASTN program. Results reflect sequences deposited through February 1998 (1,442,166 entries).

3. Chemokine Structure

Chemokines are generally small secreted proteins, 60–90 amino acids in length, that contain four highly conserved cysteine residues *(1,2,16)*. They contain a typical hydrophobic signal sequence that is cleaved off upon secretion. The three-dimensional struc-

ture of several chemokines has been determined by either X-ray crystallography or nuclear magnetic resonance *(17–22)*. Their small size and disulfide bonds serve to limit their configuration. Consequently, the monomeric structures of all chemokines are quite similar, containing a short, flexible, N-terminal domain followed by three antiparallel beta sheets connected by loops and a C-terminal alpha helix. Chemokines form dimers at high concentrations and the dimeric arrangement of CC and CXC chemokines differ. However, this appears to have little physiological relevance, as the active chemokine moiety appears to be monomeric *(23,24)*. Whereas their three-dimensional structures appear to be very similar, individual chemokines have distinct and exquisitely precise specificity for individual receptors or subsets of receptors.

3.1. CC and CXC Chemokines

Chemokines have traditionally been grouped into families based on patterns of their N-terminal cysteine residues. The CC chemokines, which comprise the largest family, contain two adja-cent cysteines near the amino-terminal end; the CXC chemokines have a single amino acid between the two N-terminal cysteines. Both families have the same disulfide linkages: the first and third cysteines form a disulfide bridge, as do the second and fourth cysteines. Although the structural differences between these two families are subtle, they correlate with significant functional differences. As a general rule, CXC chemokines are chemoattractive for neutrophils and CC chemokines for monocytes and other leukocyte subsets.

3.2. Six Cysteine Chemokines

A growing number of chemokines have six cysteines in their mature form: SLC, I-309, MPIF-1 and HCC-2. Presumably, the additional nonconserved cysteines are disulfide linked. These "6C" chemokines, however, are still considered members of the CC family because their N-terminal cysteines are adjacent and because they behave in all other respects like CC chemokines: MPIF-1 and SLC are chemoattractive for T cells *(7,11)* and I-309 is chemoattractive for monocytes *(25)*. None of the three have any effect on neutrophils. The specificity of HCC-2 has not yet been described in the literature.

The most common placement of these additional cysteine residues is between the second and third, and after the fourth con-served cysteine. The location of the additional cysteines is identical in MPIF-1 and HCC-2, suggesting a possible evolutionary relationship. SLC has a different arrangement altogether: both of the extra cysteines are located in an unusually long C-terminal extension.

3.3. Two New Families

Two recently discovered chemokines do not fit into either of the families described above and may be founding members of their own chemokine families. Lymphotactin is a "C" chemokine, which is missing the first and third cysteine residues and thus contains only a single disulfide bond *(26)*. Fractalkine is a "CX_3C" chemo-kine with three amino acids between the first two cysteines. Frac-talkine has the most divergent structure of all the chemokines described to date. The encoded gene product is 373 amino acids in length and contains a signal sequence and a chemokine domain followed by a mucin-like stalk, a transmembrane domain and a short cytoplasmic domain *(13)*. This divergent structure results in a unique and divergent function for this new chemokine as will be discussed below.

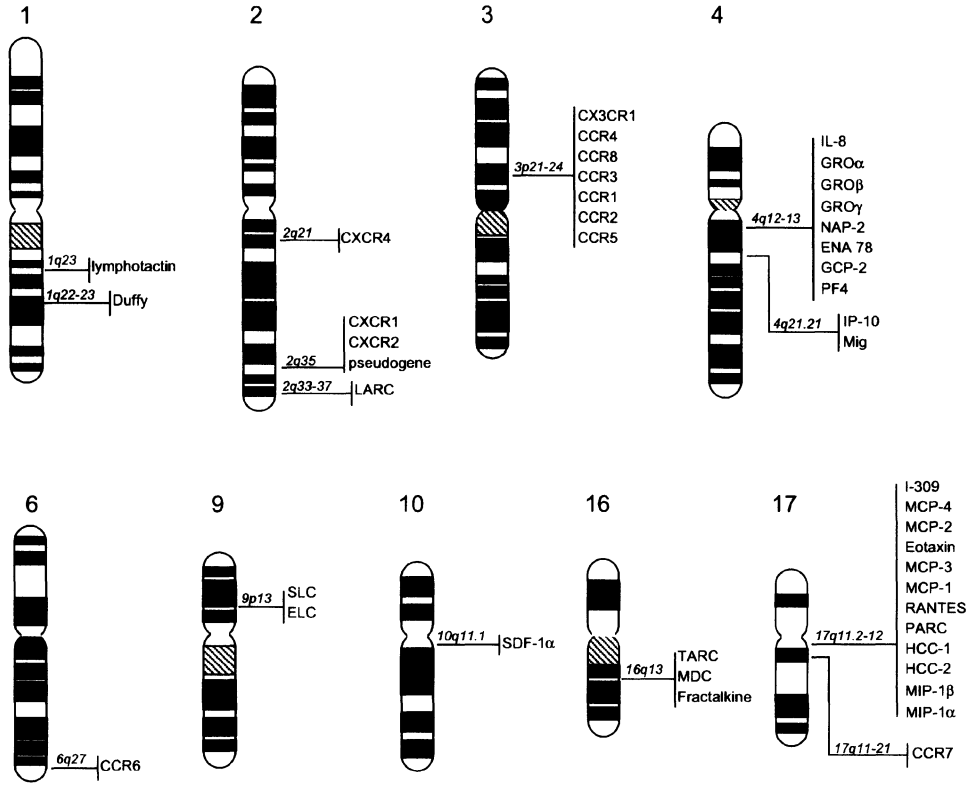

Fig. 2. Chromosomal localization of chemokine and chemokine receptor genes.

4. Chemokine Gene Localization

Until recently, the genomic organization of chemokines was simple and intuitively satisfying: the CXC chemokine genes were clustered together on chromosome 4, and the CC chemokine genes clustered on chromosome 17 *(1)*. The first indication that things might not be so simple came in 1995 when stromal cell-derived factor 1 (SDF-1) was mapped to chromosome 10 *(27)*. Today it is clear that the growing complexity of the chemokine family is also reflected in their chromosomal organization. As presented in Fig. 2, chemokine genes are now mapped to seven human chromosomes, generally clustered in groups of greatest homology. The majority of CXC genes are at *4q12–21 (1)*, but SDF-1 is found at chromosome *10q11.1 (27)*. Most CC chemokine genes are found at chromosome *17q11.2 (28)*, but at least three other chromosomes harbor CC chemokine genes: LARC is found at *2q33–37 (5)*, ELC and SLC are encoded at *9p13 (10,11)*; and MDC, TARC, and fractalkine are clustered at *16q13 (29–31)*.

4.1. Clustered Chemokines Are Closely Related

Chemokine genes within clusters are tightly linked. The chemokine gene cluster on chromosome 17 can be divided into two subregions: the MCP subfamily and the MIP subfamily *(28)*. Six chemokine genes in the MCP subfamily are clustered within 440 kb on a single yeast-artificial chromosome (YAC) *(32)*. Within the MIP subfamily, 10

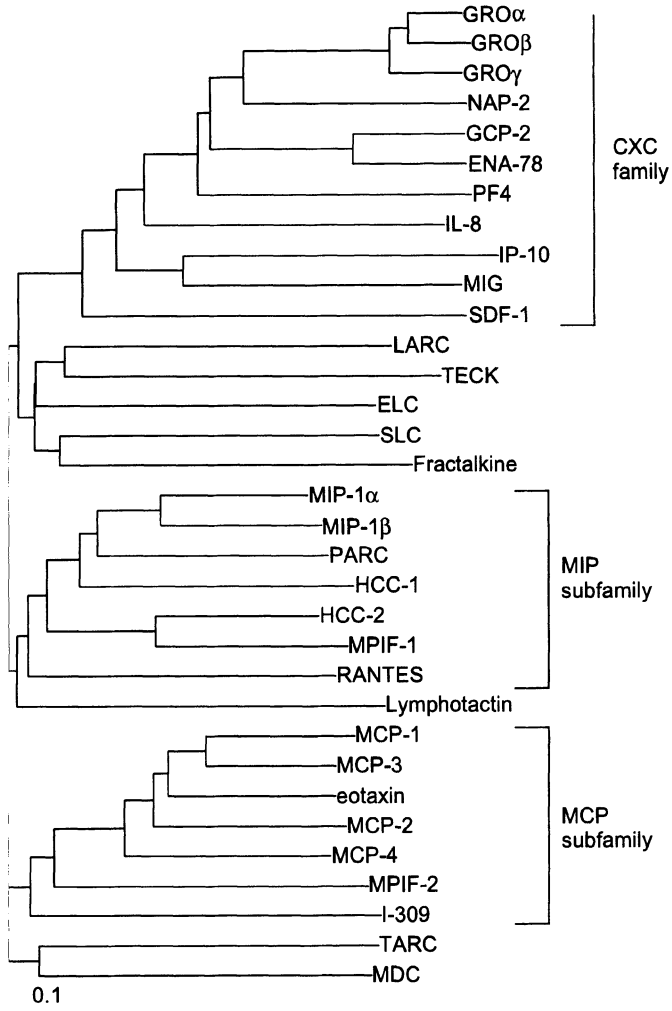

Fig. 3. Dendrogram analysis of the chemokine family. Alignment of mature chemokine sequences was generated using the Clustal W program at http://www2.ebi.ac.uk/clustalw/. The multiple alignment processor at http://blocks.fhcrc.org/blocks/process_blocks.html was used to generate the tree.

chemokine genes are contained on a single 810-kb YAC *(6)*. Such gene clustering is likely the result of recent evolutionary divergence, and consistent with this, clustered chemokines often share significant sequence homology with each other and group together when examined by dendrogram analysis, shown in Fig. 3. In addition to genetic and structural similarity, clustered chemokines generally share functional relationships: such groups of chemokines may have similar expression patterns and similar biological activities (*see* Subheading 5.1.).

4.2. Chemokine Receptors Are Also Clustered

Like their ligands, genes for chemokine receptors are also clustered, as shown in Fig. 2. Chemokine activities are mediated through G-protein-coupled receptors

(GPCRs). In addition to the 13 chemokine receptors that have currently been characterized, numerous orphan GPCRs have been identified with high similarity to chemokine receptors. Presumably, some of these orphan receptors recognize chemokines that remain to be found. CXCR4, CCR6, CCR7, CCR8, and CX_3CR1 were all first reported as orphan receptors *(33–44)*.

The GPCR superfamily may be the most diverse gene family in the human genome with at least 1000 members. These genes are spread throughout the genome, but receptors with similar function are clustered. For example, the opsin genes are clustered on the X chromosome *(45)*, four chemotactic peptide receptors are encoded on chromosome 19 *(46)*, and many odorant receptors are closely linked on chromosome 17 *(47)*. The largest cluster of chemokine receptors is found at *3p21,* where seven characterized receptor genes are located, along with several orphan GPCRs *(43)*. Human chromosome 2 encodes CXCR1, CXCR2, and a related pseudogene at *2q35 (48)* and the CXCR4 gene at *2q21 (33)*. Single chemokine receptors have been localized to chromosome 1 (*1q22–23* for the Duffy antigen) *(49)*, chromosome 6 (*6q27* for CCR6) *(39)*, and chromosome 17 (*17q12–21.2* for CCR7) *(41)*. As with their chemokine ligands, highly related chemokine receptor genes are very tightly linked. The genes for CCR1, CCR2, CCR3, and CCR5 map to within 350 kb of each other at *3p21 (50)*. The most similar of the four receptors, CCR5 and CCR2, map to within 18 kb *(51)*.

5. Chemokine Function

Although elucidation of novel chemokine sequences has been extremely rapid, unraveling their functions has been significantly more difficult. Recombinant proteins must be expressed and purified before they can be tested on leukocyte subsets for binding, calcium flux, chemotaxis, and activation. Alternatively, peptide synthesis can be utilized to produce novel chemokines for testing. In either case, the true N terminus is difficult to correctly predict, because of signal sequence processing, and the biological characterization remains difficult. Nonetheless, significant headway has been made in determining the biological roles of many of the new chemokines. Based on the identification of chemokines in disease, the known distribution of their receptors, and the in vitro chemotactic properties of these molecules, Table 2 summarizes the function of chemokines and their possible roles in human disease. Although this table contains some oversimplifications, it is useful as an aid for understanding chemokine complexity.

In general, chemokines are still primarily involved in the recruitment of leukocyte subsets to different tissues; however, the scope of their activities has been broadened from inflammation and disease states to other tasks such as lymphocyte development. In addition, several other nonchemotactic functions have been attributed to chemokines over the past few years. These new roles will be discussed in the last section of this chapter.

5.1. Refined Leukocyte Specificity

Although one could once generalize that CXC chemokines were chemoattractive for neutrophils and CC chemokines acted on mononuclear cells, a more refined picture is becoming apparent as additional chemokines are tested and characterized. Recent studies suggest that chemokines can stimulate the chemotaxis of specialized subsets of mononuclear cells. Chemoattractants specific for subsets of lymphocytes and for eosinophils and basophils are described below.

Table 2
Chemokine Receptors and Ligands

Receptors	Ligands	Function and possible disease association
CXCR1	IL-8	Neutrophil migration and activation. Acute PMN mediated disease such as ARDS, bacterial pneumonia, pancreatitis, and sepsis.
CXCR2	IL-8, GRO-α/β/γ, NAP-2, ENA-78, GCP-2	Neutrophil migration and activation. Acute PMN mediated disease such as ARDS, bacterial pneumonia, pancreatitis, and sepsis.
CXCR3	IP-10, Mig	Chemotaxis of T cells. Sarcoidosis, psoriasis, leprosy.
CXCR4	SDF-1	T cell migration to bone marrow and tissues. Graft vs. host disease, HIV/AIDS.
CCR1	MIP-1α, RANTES, MCP-2, MCP-3	T-cell and macrophage-mediated inflammatory disease such as rheumatoid arthritis and multiple sclerosis.
CCR2	MCP-1, MCP-2, MCP-3, MCP-4	Monocyte migration and activation. Atherosclerosis, bacterial and viral meningitis, rheumatoid arthritis.
CCR3	Eotaxin, RANTES, MCP-3, MCP-4, MPIF-2	Eosinophil migration and activation. Asthma, atopic allergy, and parasitic infection.
CCR4	MDC, TARC	T-cell migration and perhaps differentiation. Th2 T-cell-mediated diseases such as systemic lupus erythematosis, asthma, and atopic allergy.
CCR5	MIP-1α, MIP-1β, RANTES	Macrophage and Th1 T-cell migration. HIV/AIDS.
CCR6	LARC	T-cell and dendritic cell migration, antigen presentation.
CCR7	ELC	Lymphocyte chemotaxis. EBV-induced B-cell transformation.
CCR8	I-309	Chemotaxis of thymocytes and activated T cells.
CX3CR1	Fractalkine	Monocyte, T-cell, and NK-cell trafficking.

MDC and TARC recognize the same receptor CCR4, as shown by high-affinity binding, calcium mobilization, and chemotaxis *(29,52)*. CCR4 is predominantly expressed within the thymus, but a subpopulation of circulating T cells also express CCR4 and are capable of responding to MDC and TARC. In the periphery, CCR4 expression is restricted to Th2 $CD4^+$ T cells *(53)*. Th2 T cells make IL-4 and IL-5 following activation and are believed to be important in allergy and responses to infectious agents *(54)*. The selective expression of CCR4 by Th2 cells suggests that MDC and TARC may play an important role in the migration of T cells in allergy and infectious disease.

The recently described chemokines ELC and SLC are specifically chemoattractive for lymphocytes and not other leukocyte subpopulations *(55)*. Both are functional ligands for CCR7 *(10,56)*, a receptor formerly known as EBI1 *(40,41)*. CCR7 is selectively expressed on activated T and B lymphocytes and is strongly upregulated upon Epstein-Barr virus infection of Burkitt's lymphoma cells *(40)*.

LARC is another CC chemokine that causes chemotaxis of T cells *(5)*. LARC is expressed predominantly in liver and lung, and is recognized by CCR6, a receptor expressed in spleen and lymph nodes and found on T cells, B cells and dendritic cells *(57,58)*.

Two chemokines have recently been identified from the EST database that act on the eosinophil/basophil specific receptor CCR3. MCP-4 belongs to the MCP subfamily (60–65% amino acid identity, *see* Fig. 3) and activates both CCR2 and CCR3 *(3,59,60)*. MCP-4 has a similar expression pattern to eotaxin, being made in the lung and small intestine, target tissues for eosiniphils. MPIF-2 (39% identical to eotaxin) selectively activates CCR3 and eosinophils *(61,62)*. Expression of these chemokines would therefore be expected to lead to a cellular infiltrate enriched for eosinophils and basophils, such as is seen in allergic inflammation.

5.2. Chemokines in the Thymus

Four chemokines have recently been described that are predominantly expressed in the thymus: PARC, TARC, MDC, and TECK *(6,8,9,12)*. The chemokine receptors CCR4 and CCR8 are also expressed principally in the thymus *(52,63)*. These observations suggest that chemokines may play an important role in thymocyte migration, differentiation, and education. During T-cell development in the thymus, a complex developmental program takes place that includes the expression and rearrangement of the T-cell-receptor genes, commitment to the CD4 or CD8 lineage, and the elimination of T cells which respond to "self" antigens by apoptosis *(64)*. These processes are spatially and temporally regulated. Immature, bone-marrow-derived, T-cell progenitors enter the subcapsular region of the thymus, and migrate into the thymic cortex and then into the medulla before exiting to the periphery *(65)*. The generation of mature T lymphocytes therefore requires the migration of specific subsets of cells to appropriate anatomical sites within the thymic microenvironment, a process that may be chemokine mediated.

The diversity of chemokine and chemokine receptor expression within the thymus may reflect the diversity of cell types generated during T-cell development. Selective expression of chemokines and their receptors would allow for the specific migration of subsets of developing T cells. TECK has been reported to be chemotactic for thymocytes and is expressed by thymic dendritic cells *(12)*. MDC (and presumably TARC) is chemotactic for a subset of $CD4^+$ $CD8^+$ thymocytes that express CCR4 (D. Chantry, C. J. Raport, and P. W. Gray, unpublished observations). Another thymic chemokine, I-309, is a potent antagonist of dexamethasone-induced apoptosis of murine thymomas *(66)*. Definition of the role that specific chemokines and their receptors play during T-cell development will require determination of their in vivo localization as well as a study of the consequences of the inactivation of these genes in the mouse germ line by homologous recombination.

5.3. Novel Functions

In addition to being chemoattractive for specific subsets of leukocytes, chemokines often have other biological functions. Chemokines such as HCC-1 and SDF-1 may play a role in tissue homeostasis as they are expressed constitutively in many tissues and HCC-1 is present at high concentrations in normal plasma (1–10 n*M*). Other chemokines are known to modulate angiogenesis *(16)* and hematopoiesis *(67)*. Several of the new chemokines also fall into this category and will be discussed below. The interesting development that several chemokines play a major role in HIV pathology will also be discussed below, as well as the possibility that a chemokine can act as an adhesion molecule.

5.3.1. Role in Hematopoiesis

Several of the new chemokines—MPIF-1, MPIF-2, LARC, and SLC—have been shown to be not only chemoattractants for leukocytes, but also inhibitors of hematopoietic progenitor-cell proli-feration. These dual functions put them in a class with several other established chemokines, including MIP-1α *(68)*, MCP-1, platelet factor (PF)-4, IL-8, and GRO-β *(67)*.

MPIF-1 and MPIF-2 were identified as ESTs with high homology to MIP-1α (51 and 42% identity, respectively). MPIF-1 acts as a chemoattractant primarily for resting T cells and monocytes *(7)*, whereas MPIF-2 is specific for eosinophils and basophils *(61,62)*. MPIF-1 and MPIF-2 showed similar activities in human hematopoietic progenitor-cell colony-formation assays. They both had an inhibitory effect on the committed progenitors that give rise to granulocyte and monocyte lineages (CFU-GM) as well as on the multipotent hematopoietic precursors (CFU-GEMM), but no effect on erythroid or megakaryocyte precursors *(7)*.

LARC and SLC were also identified as ESTs that are highly related to each other, though SLC has a long C-terminal extension that is unique among CC chemokines. LARC was found to be chemotactic for lymphocytes *(5)* and monocytes *(69)*, whereas SLC was chemotactic only for lymphocytes *(11,70)*. LARC and SLC were shown to have similar potency to MIP-1α in inhibiting colony formation by human hematopoietic progenitors CFU-GM (colony-forming unit-granulocyte-macrophage) and CFU-GEMM (granulocyte-erythroid-monocyte-megakaryocyte). LARC and SLC also inhibited colony formation by human erythroid progenitor cells (BFU-E) *(69,70)*.

5.3.2. Chemokines as HIV Suppressive Factors

One of the most exciting developments over the past few years has been the discovery that chemokines and chemokine receptors play a role in HIV pathology. Although CD4 was initially characterized as the receptor for the HIV-1 virus, it was known that an additional coreceptor was necessary for viral entry into a $CD4^+$ cell. In 1996, CXCR4 and CCR5 were identified as primary coreceptors for HIV-1 entry *(71–76)*. It had previously been reported that certain chemokines secreted from $CD8^+$ T cells, MIP-1α, MIP-1β, and regulated upon activation, normal T cell expressed and secreted (RANTES), could act as potent viral suppressive factors for HIV-1 *(77)* and that levels of these three chemokines were elevated in individuals who remained uninfected after multiple exposures to the HIV-1 virus *(78)*. However, the mechanism of chemokine inhibition was unknown. Since that time, several other chemokine receptors have been shown to function as coreceptors for subsets of HIV-1 isolates, including CCR2b, CCR3, and CCR8 *(75,76,79)*. Chemokines that are the natural ligands for these coreceptors, when present in high enough concentrations, interfere with HIV-1 entry by occupying the receptors and thus blocking the interaction between the virus and its corecep-tor. More recently, MDC has also been identified as an HIV-1-suppressive factor *(80)*. It is interesting to note that CCR4, the only known receptor for MDC *(29)*, is not a coreceptor for HIV-1 *(79)*. This raises the possibility that chemokines may affect the viral life cycle at other points besides entry into the cell. It is currently believed that chemokines or chemokine analogs may prove to be useful therapeutics for the treatment of AIDS *(81,82)*.

5.3.3. Can a Chemokine Act as an Adhesion Molecule?

Fractalkine, the most structurally divergent of all chemo-kines, exists as a membrane-bound glycoprotein in which the chemokine domain sits on a mucin-like stalk

(13). Fractalkine can also be cleaved, presumably by proteolysis, to generate a soluble form of the molecule. A receptor for fractalkine has recently been identified and named CX_3CR1 *(83)* (previously known as V28) *(44)*. The chemokine domain of fractalkine was shown to be necessary and sufficient for high-affinity binding and chemotaxis through CX_3CR1. Adhesion of CX_3CR1-expressing cells to fractalkine was seen only when the chemokine and mucin domains were physically linked. These findings suggest that in the context of appropriate presentation a chemokine-chemokine receptor interaction is sufficient to mediate cell adhesion in the absence of integrins or selectins *(83)*. The fractalkine gene is closely linked to MDC and TARC at *16q13*, suggesting that fractalkine is more functionally related to CC chemokines than other chemokine subgroups. Consistent with this, the CX_3CR1 gene lies near the CC chemokine receptor cluster at *3p21*. Both fractalkine and its receptor are expressed in lymphoid tissues, but surprisingly both are also expressed in the brain. Whereas the neural function of chemokines remains to be determined, it is interesting to speculate that they may play important roles in neuronal migration, homeostasis, or differentiation. Alternatively, chemokines in the brain may regulate function of glial cells.

6. Conclusions

This is an exciting time to be working in the field of chemokine biology. With the advent of the Internet and easy access to vast databases of randomly sequenced cDNAs, the number of known chemokines is rapidly increasing *(84)*. Trailing only somewhat behind is our understanding of the diverse roles that chemokines play in human physiology. Their relatively small size and highly conserved cysteine residues make chemokines ideal targets for recog-nition in the EST database. Their ever-expanding roles in immune function and disease make chemokines interesting targets to investigate and we can expect both the family size and the functions they play to grow in the years ahead.

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