Commentary

Chemokine Receptors and T Cell Chemotaxis

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The migration of T cells is a highly regulated process, serving to distribute functional subsets of cells to the appropriate tissue or microenvironment. The role of adhesion molecules in this process is well appreciated (1, 2) however an additional class of molecules, the chemoattractant cytokines (chemokines) and their receptors, are now receiving considerable attention, because of their fundamental role not only in leukocyte migration, but also in hematopoiesis, T cell activation, and leukocyte degranulation (3). In addition, a recent flurry of papers has demonstrated that chemokine receptors act as cofactors for HIV-1 entry into cells (reviewed in references 4, 5). Two papers in the current issue of this journal add significantly to our understanding of the role of chemokines and their receptors in T cell traffic.

There are two major families of chemokines, termed CXC and CC according to the presence or absence of an amino acid between a pair of cysteine residues near the NH_2 terminus. One of the first members of the chemokines to be identified was IP-10, in 1985 (6), and now 40 or more are known to exist. The first receptors for chemokines were identified several years ago (7, 8), and were found to be seven transmembrane spanning receptors (7TMR), that signal through G protein interactions (3, 9, 10). 7TMR also function for the classical chemoattractants, such as fmlp and C5a (11), and also for the chemotaxis of primitive species such as *Dictyostelium* (12).

The human chemokine receptors that have been defined to date are listed in Table 1. The precise expression of many of these receptors is not yet known, because specific mAbs are not available. For T cells, PCR or northern blotting indicates that the five known receptors for CC chemokines, defined as CCR1 to CCR5 (A new nomenclature for CC and CXC chemokine receptors was adopted at the 1996 Gordon Research conference on chemotactic cytokines. See Table 1.), are expressed on subsets of T cells. Delineating exactly which subsets is an area of intense study, because chemokine receptor expression may explain the localization or migration of various cell types, such as TH1 or TH2 T cells, or tissue homing subsets. It may also determine which T cells are infected with different strains of HIV-1. A surprising finding is that, within the T lineage, many of the known chemokine receptors are restricted to activated or memory ($CD45RO^+$) type cells. The exact nature of $CD45RO^+$ T cells is still unclear (13), however they do show major differences from $CD45RA^+$ T cells with respect to adhesion properties in vitro, and migration patterns in vivo (13, 14). The MCP-1 receptor (CCR2) is expressed on the $CD26^{hi}$ $CD45RO^+$ T cell subset, and it is these T cells that respond to MCP-1 in chemotaxis assays (15, 16). Likewise, T cells responding to RANTES in chemotaxis assays are of the memory phenotype (17), suggesting that the RANTES receptors (CCR1, CCR4, or CCR5) are restricted to this type of T cell. Some of the orphan receptors show a similar pattern. BLR-1, which has similarity to the CXC receptor family, is expressed on a subset of $CD45RO^+$ T cells, as well as on B cells (18). The two IL-8 receptors, CXCR1 and CXCR2, are restricted to NK-like cells within the T lineage (16). However most of the chemokine receptors are expressed by several leukocyte types, and can also be expressed on epithelial cells or neuronal cells.

A New CXC Receptor Restricted to Activated T Cells

In this issue, Loetscher et al. (19) describe a third CXC chemokine receptor, designated CXCR3 (Table 1). CXCR3 is a 7TMR that signals in response to the CXC chemokines IP-10 and Mig. Several features of CXCR3 and its ligands IP-10 and Mig are particularly noteworthy. First, CXCR3 is highly restricted to activated T cells and NK cells, and not other leukocytes, unlike most of the other receptors (Table 1). Thus IP-10 or Mig signaling is potentially an important mechanism for selective homing of activated/effector cells, which preferentially accumulate in some inflammatory sites (20), as well as in many tumors. There is a clear rationale to focus effector T cells to these sites, since this is where an effector arm of the T cell immune system is needed. Once T cells gain entry to a tissue, IP-10/Mig-CXCR3 interaction may also be important to position effector T cells, for instance close to the inflammatory stimulus, or within a tumor.

A distinguishing feature of IP-10 and Mig is that they are both highly inducible by γ interferon or LPS. Indeed IP-10 was one of the first chemokines to be identified, through its induction in various cells by γ interferon (6). Until recently, the significance of IP-10 has been unclear, since no clear function could be ascribed to it. IP-10 was found, somewhat contentiously, to specifically attract activated T cells (21), and this has now been confirmed by Loetscher et al. (19). Mig, which is a close relative of IP-10, was found to act selectively on tumor infiltrating T cells and activated T cells (22). Little is known about the expression of Mig, but IP-10 is expressed abundantly in certain inflammatory lesions, particularly those characterized by T cell infiltration, such as delayed type hypersensitivity responses in skin (23), and in EAE (24).

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Table 1. *Chemokine Receptors, Their Ligands, and Their Predominant Expression Pattern on Leukocytes*

Chemokine receptor	Old names	Ligands defined to date	Predominant expression
CCR1	CC CKR1	MIP-1α, RANTES, MCP-3	Mono, T,
CCR2a,b	MCP-1Ra,b	MCP-1, MCP-3, MCP-4	Mono, T, baso.
CCR3	CKR-3	eotaxin, RANTES, MCP-2,3,4	Eos, baso.
CCR4		RANTES, MIP-1α, MCP-1	Baso., T
CCR5	CC CKR5	RANTES, MIP-1α, MIP-1β	Mono, T,
CXCR1	IL-8 RA, IL-8 R1	IL-8	Neutrophils, NK
CXCR2	IL-8 RB, IL-8 R2	IL-8, GROα, NAP-2, ENA-78	Neutrophils, NK
CXCR3	None	IP-10, Mig	Act. T
CXCR4	Fusin/humstr/Lestr	SDF-1	Widely expressed
No designation	BLR-1	?	B, memory T
"	BLR-2/EBI1	?	B, act. T
"	V28	?	

eos, eosinophils; *baso.*, basophils; *mono*, monocytes; *act. T*, activated T cells; *B*, B cells.

SDF-1, an Unusual CXC-like Chemokine

IP-10/Mig interaction with CXCR3 clearly establishes that CXC chemokines are important for the migration of T cells, and not just granulocytes. A second report in this issue (25) shows that a CXC-like chemokine, stromal cell-derived factor 1 (SDF-1) is actually one of the most efficacious chemokines for T and B cell migration i.e., it attracts a high percentage of these cells. SDF-1 was originally noted for its effects on B cell proliferation (26) but it clearly has functions on other cell types, even outside the immune system. Technically SDF-1 belongs to the CXC family, although it shows equidistant sequence homology to CC and CXC chemokines, and is highly conserved in evolution suggesting that it may be a primordial chemokine. The constitutive expression of SDF-1 in a broad range of tissues (26) prompted Bleul et al. (25) to speculate that SDF-1 may be relevant for basal trafficking of cells, rather than for inflammation. The efficacious attraction of T cells by SDF-1 indicates that the receptor for this chemokine, might be much more widely expressed than most of the other chemokine receptors such as CCR1 through CCR5, or CXCR3. The receptor for SDF-1 has just been identified as LESTR/fusin (26a, 26b), a little studied, 7TMR which gained notoriety recently because of its role as a coreceptor for HIV infection (26c). SDF-1 is a potent inhibitor of infection by lymphocyte-tropic HIV-1 strains. The reason why LESTR/fusin (now termed CXCR4, Table 1) and CCR5 are so important for HIV entry is uncertain, although it may relate to their levels of expression on T cells and monocytes. SDF-1 and its receptor might be involved in lymph node homing by lymphocytes. Lymphocyte migration across high endothelial venules is pertussis toxin sensitive (27), indicating the involvement of a G protein coupled 7TMR.

Chemokine Receptor Expression on T Cells Is Tightly Regulated

Apart from the SDF-1 receptor, most of the chemokine receptors are upregulated on activated/memory subsets of T cells. This appears to relate to the effects of IL-2. IL-2 was found to upregulate markedly the expression of CCR1 and CCR2 on $CD45RO^+$ T cells when activated in vitro, and this correlated with the ability of these T cells to respond to RANTES and MCP-1 in chemotaxis assays (28). This induction of responsiveness was not related simply to activation, since exogenous IL-2 was obligatory. This effect of IL-2 could be partially mimicked by IL-4, IL-10, or IL-12. The IL-2 effect may explain the restricted expression of many of the chemokine receptors, since activation and induction of high affinity IL-2 receptors may be a prerequisite for receptor upregulation. This has implications for at least two fields of human health. HIV uses chemokine receptors as cofactors for cell entry, which suggests that activated, IL-2-stimulated T cells, which are abundant during normal immune responses, would be the cells targeted for infection by the virus. Memory $CD4^+$ T cells, which are the descendants of activated T cells, are selectively lost in HIV-1-infected individuals (29). Another important consideration is that IL-2 therapy is used for the treatment of various tumors in humans. IL-2 treatment in humans or mice leads, in many cases, to a multiple organ lymphocytic infiltration (30), which probably relates to chemokine receptor induction.

Chemokines steer cells in the right direction, however adhesion molecules play a critical role in the selective adhesion of T cell subsets to inflamed endothelium. α4, β1, β7 or β2 integrins, or P- and E-selectin ligands, mediate adhesion of blood-borne cells to inflamed endothelium, particularly subsets of memory and activated T cells which express

the highest levels of these molecules (20). Since the development of the multi-step paradigm of leukocyte binding to blood vessel endothelium (1, 2, 31), chemokines have been proposed as one of the signaling elements for integrin activation, which could act combinatorially with adhesion molecules to determine leukocyte traffic to tissues (31). This might be especially important for relatively restricted receptors, such as the IL-8 receptors on neutrophils (3) and the eotaxin receptor (CCR3) on eosinophils (32). Chemokines, as well as classical chemoattractants, can certainly signal integrin mediated adhesion of cells to ICAM-1 or VCAM-1 (33, 34). Recent studies suggest that firm adhesion triggering via chemokine receptors appears to require high numbers of receptors on the cell surface (34), which is the case for the IL-8 receptors on neutrophils, or the eotaxin receptor on eosinophils (~60,000 receptors per cell). Chemokine receptor levels on T cells usually number only 1,000–4,000, at least for the receptors characterized so far, which may explain why chemokines acting on T cells appear more important for transendothelial migration or chemotaxis within a tissue, rather than integrin activation on blood vessel endothelium (34, 35).

Whatever their point of action is, blocking chemokine function has profound effects on inflammatory responses. MIP-1α-deficient mice have impaired immune responses to certain viral infections (36), and anti-MIP-1α administered to mice markedly affects the recruitment of immune cells to a variety of inflammatory sites (37). Similarly, anti-IL-8 in various animal models of ischemic reperfusion injury inhibits neutrophil recruitment and decreases tissue damage (37), and anti-MCP-1 in rats inhibits DTH-mediated inflammation (38). The chemokines are important components of the immune response, and the recent knowledge of their actions provides a basis for designing new therapies for a variety of human diseases.

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