REVIEW: CHEMOKINES

Chemokines and Cell Migration in Secondary Lymphoid Organs

Jason G. Cyster

As few as one in 100,000 B and T lymphocytes are specific for a single protein antigen, such as tetanus toxin, yet these cells must come together if an antibody response is to occur. Bringing antigen-presenting cells and rare antigen-specific B and T lymphocytes into physical contact is a principal function of secondary lymphoid organs. In the last few years, details have begun to emerge on the cues that guide cell movements inside lymphoid organs, and a central role for the chemokine family of molecules has been uncovered. Here, current understanding of the roles played by chemokines in the functional biology of secondary lymphoid organs will be reviewed.

For much of this century it has been known that the secondary lymphoid organs, lymph nodes, spleen, tonsils, and Peyer's patches, are the sites where immune responses against microbes and other foreign particles (or "antigens") are initiated (*1*). Specialized transport systems carry antigens from peripheral sites of entry into each of the secondary lymphoid organs. Antigens entering across the skin are carried by lymphatic vessels into lymph nodes, those entering the gastrointestinal tract are ferried by specialized epithelial cells into tonsils and Peyer's patches, and blood-borne antigens are filtered and concentrated within the spleen. After being released from the primary lymphoid organs, bone marrow and thymus, lymphocytes migrate rapidly from the bloodstream into secondary lymphoid organs (*1*). By being almost continually on the move, individual lymphocytes are able in a matter of days to survey many of the secondary lymphoid organs in the body for the presence of their specific antigen. The survey process involves B cells and T cells migrating (or "homing") to separate compartments within the secondary lymphoid organ, called B cell follicles and T cell areas (Fig. 1), staying for several hours, and then migrating back into circulation. When foreign antigen is detected, a new and more complex series of movements begins, leading to a kind of "cellular dance" that helps bring antigen-specific B and T cells together for an immune response. Many of the cues needed for this cellular dance are provided by members of the chemokine family.

The Chemokine Family

Chemokines are small chemoattractive proteins found in mammals, birds, and fish (*2*). Four subtypes have been identified (Table 1), named after the number and spacing of cysteine residues in the amino-terminal region as C, CC, CXC, or CX_3C. All are secreted molecules except the single defined CX_3C chemokine, fractalkine, which has transmembrane and cytoplasmic domains (*2*). Chemokines are highly basic proteins, a feature they share with other factors that function in gradients such as the axon-guiding netrins (*3*), and this property may help mediate stable gradient formation by promoting interactions with sulfated proteins and proteoglycans. Chemokines signal through transmembrane receptors that cross the cell membrane seven times and that couple to heterotrimeric GTP–binding proteins (G proteins) (Table 1). Induction of migration up a chemokine gradient (chemotaxis) requires activation of pertussis toxin (PTX)–sensitive G proteins (G_i) (*4*). The first chemokines were identified as molecules induced at sites of inflammation, where they function to recruit granulocytes, monocytes, immature dendritic cells, and activated T cells (*5*). Some also activate cells for the respiratory burst or induce release of inflammatory mediators. Different tissues produce different repertoires of "inflammatory chemokines," and this helps to attract appropriate subsets of effector cells into the tissue to respond to the particular pathogen or type of tissue damage (*5*). More recently, chemokines have been identified that are expressed constitutively within lymphoid organs and that attract naïve as well as activated lymphocytes (*2*). These "lymphoid chemokines" and their receptors appear to be critical for the homeostatic trafficking of leukocytes into subcompartments of lymphoid organs. This review focuses on the role of chemokines in secondary lymphoid organs, but it should be noted that important functions are also emerging for these molecules in bone marrow and thymus (*2*).

Department of Microbiology and Immunology, University of California San Francisco, San Francisco, CA 94143, USA. E-mail: cyster@itsa.ucsf.edu

Lymphoid Organ Entry

Lymphocyte passage across endothelium into lymph nodes and Peyer's patches is a multistep process that involves selectin-supported rolling, followed by a triggering event, and then firm integrin-mediated adhesion (*6*). The finding, more than a decade ago, that the triggering event was PTX sensitive (*7*) led to a quest for chemokines that were expressed on high endothelial venules (HEVs) in the lymph node and that could account for the mass transit of resting lymphocytes across these specialized vessels (Fig. 1). The best candidate is the CC chemokine, secondary lymphoid tissue chemokine (SLC) also called 6Ckine (*8*), which is expressed by HEVs and is active in inducing integrin-mediated adhesion of naïve lymphocytes (*8, 9*). A central role for SLC in T cell migration across HEVs was suggested by the observation that mice homozygous for a spontaneous mutation, *plt* (paucity of lymph node T cells), lack SLC expression in lymphoid organs and have defective T cell trafficking into lymph nodes (*10*). This role has been further supported by the demonstration that when T cells lack the SLC receptor, CCR7 (*11*), they have a markedly reduced ability to enter lymph nodes and

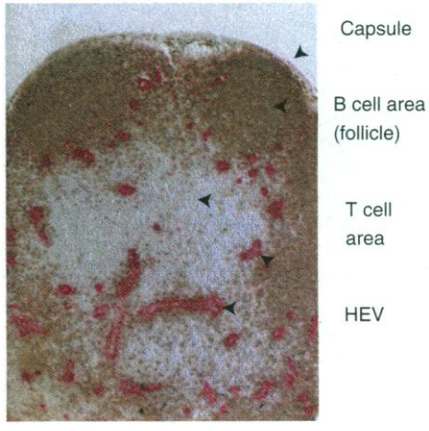

Fig. 1. Compartmentalization of B and T lymphocytes in a secondary lymphoid organ. A one-cell-thick section of mouse lymph node was stained to detect B lymphocytes (brown) and high endothelial venules (HEVs, red). Light blue counterstaining shows the T cell area. Note that, although small numbers of B cells are located near HEVs, probably having just migrated into the lymph node from the blood, most are well separated from the T cells in a lymphoid follicle.

Peyer's patches (*12*). B cell trafficking in *plt* mice and in CCR7-deficient mice is less affected than T cell trafficking, indicating a dichotomy in the requirements for B and T cell entry into lymph nodes and Peyer's patches and suggesting that a further chemokine may exist on HEVs that promotes adhesion of rolling B cells (*10, 12*). After chemokine-induced integrin activation and firm adhesion, cells migrate rapidly across the endothelium. Adhesion molecule distribution helps direct the migrating cells (*6*), and further guidance is likely provided by chemokines emanating from inside the lymphoid organ.

Compartmental Homing

Once naïve lymphocytes have crossed the endothelium in lymph nodes and Peyer's patches or have been released from terminal arterioles in the spleen, B cells localize efficiently in B cell areas (follicles), and T cells in T cell areas (Fig. 1). Evidence for chemokine involvement in homeostatic trafficking to these compartments came from studies on an orphan chemokine receptor (BLR-1, now called CXCR5) that is expressed by recirculating B cells (*13*). Targeted inactivation of CXCR5 led to a defect in the development of B cell follicles in spleen and Peyer's patches, and transfer of CXCR5-deficient B cells to wild-type recipients established that the cells suffered an intrinsic defect in their capacity to migrate to splenic follicles (*13*). These studies directly implicated the follicle as a source of CXCR5 ligand, and this attractant was identified during characterization of novel chemokine-related sequences (*14*). Termed B lymphocyte chemoattractant (BLC) or B cell–attracting chemokine (BCA)-1, in situ hybridization analysis showed this CXC chemokine is constitutively expressed by resident stromal cells, most likely a subset of follicular dendritic cells (FDCs), in lymphoid follicles of all secondary lymphoid organs (*14*; see Fig. 2). Normal development and function of FDCs require signaling by the cytokines lymphotoxin (LT)-$\alpha_1\beta_2$ and tumor necrosis factor (TNF) (*15*), and expression of BLC has been found to depend strongly on these cytokines (*16*). In in vitro chemotaxis assays, BLC attracts mature B cells and small numbers of T cells (*14*). CXCR5 and BLC therefore represent a receptor-ligand pair that helps mediate compartmental homing of B lymphocytes.

The involvement of chemokines in guiding cell movements within the T cell area is also now well established. SLC, in addition to being expressed by lymphoid endothelial cells, is expressed by stromal cells within T cell areas of lymph nodes, spleen, and Peyer's patches (*8, 17*; see Fig. 2). A second ligand for CCR7, Epstein-Barr virus–induced molecule 1 ligand chemokine (ELC) [also called macrophage inflammatory protein-3β (MIP-3β)] is also expressed in T cell areas (*18*; Fig. 2). ELC can be made by macrophages, dendritic cells (DCs), and some nonhematopoietic cells, and the relative contribution of hematopoietic and nonhematopoietic cells to expression in T cell areas remains to be defined (*18, 19*). In in vitro chemotaxis assays, SLC and ELC are efficacious attractants of resting T cells and weaker attractants for B cells. Expression of both SLC and ELC is markedly reduced in the spontaneous mutant mouse strain, *plt*, and, in addition to the defective entry of cells across HEVs, the organization of cells in T cell areas is severely disturbed in these mice. Although the precise mutation in *plt* mice has not yet been defined, the importance of SLC or ELC or both in the movement of lymphocytes and DCs through T cell areas of spleen, lymph nodes, and Peyer's patches has been confirmed by findings in CCR7-deficient mice (*12*). Insight into the regulation of SLC and ELC expression has come from the finding that expression in the spleen is strongly dependent on signaling by LT-$\alpha_1\beta_2$ (*16*). SLC is also decreased in mice deficient in RelB, a member of the nuclear factor NF-κB family of transcription factors (*17*), consistent with the possibility that LT-$\alpha_1\beta_2$ promotes chemokine expression by inducing NF-κB activity. It remains to be established why two chemokine ligands for a common receptor are expressed in a similar location, but it can be proposed in the case of lymph nodes that, once SLC has triggered T cell binding to HEVs, ELC is needed together with SLC to attract the cells into the T cell area.

Finding the Right Partner During the Immune Response

Dendritic cell migration. A critical event in the initiation of most immune responses is for DCs to migrate from the infected peripheral tissue to the draining lymphoid organ, bearing antigens derived from the infecting agent (*20*). The best characterized example is the migration of Langerhans' cells from the skin epidermis into dermal lymphatics and subsequently deep into the T cell area of lymph nodes to become antigen-presenting DCs (*20*). As part of their maturation program that leads to becoming DCs, Langerhans' cells up-regulate expression of CCR7 and become responsive to SLC and ELC (*20*). At the same time, they decrease expression of receptors for chemokines [such as MIP-1α, interleukin-8 (IL-8), and MIP-3α] that are made in inflamed tissues. Maturing DCs undergo a rapid burst of inflammatory chemokine synthesis, and it is suggested that they deposit large amounts of chemokine in the local tis-

Table 1. Mouse chemokine receptors and their ligands. Not all names for a given chemokine are listed, but those that follow in parentheses are names for the preceding chemokine. CXCR1 and several chemokines, including IL-8 and DC-CK1, have been identified in humans but not in mice. Chemokines without known receptors are not listed. For more information on chemokine nomenclature, see (*2*).

Receptors	Ligands
	CXC chemokines
CXCR2	GRO (KC), LIX (GCP2), MIP-2
CXCR3	MIG, crg-2 (IP-10)
CXCR4	SDF-1 (PBSF)
CXCR5	BLC (BCA-1)
	CC chemokines
CCR1	MIP-1α, RANTES, MARC (MCP-3)
CCR2	JE (MCP-1), MARC (MCP-3), MCP-5
CCR3	Eotaxin, RANTES, MIP-1α
CCR4	MDC (ABCD-1), TARC
CCR5	RANTES, MIP-1α, MIP-1β
CCR6	MIP-3α (LARC, Exodus)
CCR7	SLC (6Ckine), ELC (MIP-3β)
CCR8	TCA-3 (I-309)
CCR9	TECK
	C chemokine
XCR1	Lymphotactin (SCM-1)
	CX_3C chemokine
CX_3CR1	Fractalkine (neurotactin)

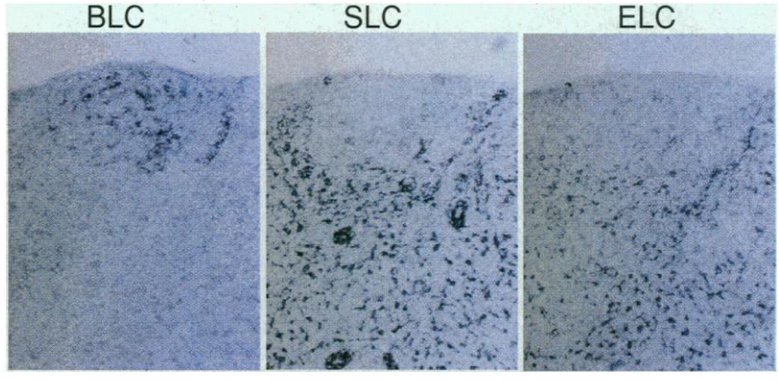

Fig. 2. Lymphoid chemokine expression in mouse lymph node. Adjacent sections were hybridized with RNA probes specific for BLC, SLC, and ELC, as indicated. Signal is seen as black staining. The BLC signal is localized in B cell follicles; the SLC and ELC signals are limited to the T cell area. Note that in addition to isolated cells, ringlike structures that correspond to HEVs can be seen hybridizing with the SLC probe.

sue environment to help attract other cells to the site (including more immature DCs) before themselves departing to the lymphatics (*21*). The CCR7 ligand, SLC, in addition to being made within lymphoid organs, is also expressed by lymphatic endothelium (*8*), and recent findings favor a role for SLC and CCR7 in entry of DCs into lymphatic vessels (*22*). Having entered lymphatics, maturing DCs then pass into the subcapsular sinus of lymph nodes and from there migrate into T cell areas. This trafficking step also appears to involve SLC (and possibly ELC), since DC migration to T zones is decreased in *plt* mice and CCR7-deficient mice (*10, 12*). In in vitro chemotaxis assays, maturing DCs are up to 1000 times as sensitive to SLC as T cells (*23*), a difference that may be important in allowing DCs to migrate quickly into the central T zone.

Dendritic cell–T cell encounters. For mature DCs to function in an immunogenic manner, it is important that they interact rapidly with antigen-specific T cells (Fig. 3). This might be promoted not only by the DCs migrating to the area of the lymphoid organ richest in T cells, but also by the DCs themselves expressing T cell–attracting chemokines. Expression of ELC has been detected in some types of DCs (*18, 19*), and the weaker naïve T cell attractant, DC-CK1 (dendritic cell–derived C-C chemokine), also called PARC (pulmonary and activation-regulated cytokine), is also expressed by some DCs in human lymphoid organs (*24*). Attraction of naïve T cells may help ensure that antigen-presenting DCs interact rapidly with multiple T cells, allowing efficient scanning for cells that recognize the antigen. DC attraction of resting T cells may also function in maintaining peripheral homeostasis as T cell survival is dependent on repeated interactions with cells bearing major histocompatibility complex (MHC)–self-peptide complexes (*25*). Many chemokines attract subsets of activated, but not naïve, T cells (*2, 5*), and some of these probably also function in promoting DC–T cell interactions. This includes RANTES (regulated-upon-activation, normal T expressed and secreted), IP-10 (interferon-inducible protein-10), TARC (thymus and activation-regulated cytokine), and MDC (macrophage-derived chemokine), chemokines found to be up-regulated for prolonged periods after in vitro DC maturation (*21*). In vivo, Langerhans' cells have been found to up-regulate attractants of activated T cells, including MDC, as they migrate into the lymph node T cell zone to become antigen-presenting DCs (*26*).

A question that arises from these studies showing that maturing DCs make chemokines that attract activated T cells is what is the significance for the immune response? One possibility is that it enhances the rate of T cell clonal expansion. Maturing DCs and naïve T cells may initially be attracted together in the T cell zone by SLC, ELC, and other directional cues. In addition, antigen may be acquired by other DCs that preferentially interact with naïve T cells. Once some T cells become activated, these cells or their daughters may then migrate more efficiently than the surrounding naïve T cells (most of which are of incorrect specificity) toward newly arriving DCs expressing chemokines such as MDC. In this way, the rate of encounter between antigen-bearing DCs and antigen-specific T cells might be accelerated relative to the rate that would occur if maturing DCs attracted naïve and activated T cells equally. This process may become especially important as the T cells divide and saturate available niches on the priming DCs or if the priming DCs undergo cell death (*20*). The finding that many activated T cell attractants differ in the efficiency with which they attract cells of T helper (T_H)-1 or T_H2 cytokine-secreting phenotype (*27*) also points to a role for DC chemokine expression in promoting polarization of T cell responses. Furthermore, expression of the transmembrane chemokine, fractalkine, by DCs suggests that chemokines may function in promoting adhesion between DCs and T cells (*28*). The importance of SLC, ELC, and CCR7 in bringing DCs and T cells together for the T cell immune response has been supported by studies in *plt* mice and CCR7-deficient mice (*10, 12*). Future studies in mice lacking other chemokine- and chemokine receptor genes are certain to help determine the importance of chemokine expression by DCs in clonal expansion and differentiation of T cells.

T cell–B cell encounters. While events are unfolding in the T zone, another well-choreographed set of movements takes place in and around the B cell area (Fig. 3). B cells may first encounter antigen in any of several locations: in the blood; in areas of lymph node near HEVs, where antigen has been shown to flow from the subcapsular sinus via collagenous conduits; within the marginal zone of the spleen, a site of high blood flow; or on the surface of antigen-transporting cells or FDCs within follicles (*29*). Once the B cell has bound sufficient antigen, it is redirected from the migration route of naïve B cells and instead moves to the boundary of the B and T cell zones (*30, 31*). Some differences exist in the precise positioning of antigen-engaged B cells in spleen compared with lymph nodes (*30–32*), but in both cases, the cells end up in a location accessible to T cells. In in vitro studies, B cell receptor (BCR)–stimulated B cells have increased responsiveness to ELC and SLC, providing a possible mechanism for the increased T-zone tropism of the cells (*18*). In addition to promoting migration to the outer T zone, BCR stimulation promotes B cell expression of MIP-1α, MIP-1β, and MDC (also called ABCD-1, activated B cell and dendritic cell CC chemokine) (*33*), chemokines that are effective in attracting activated T cells (*2, 5, 26*). Production of these chemokines may enhance the chance of encounter between antigen-specific T cells and antigen-presenting B cells.

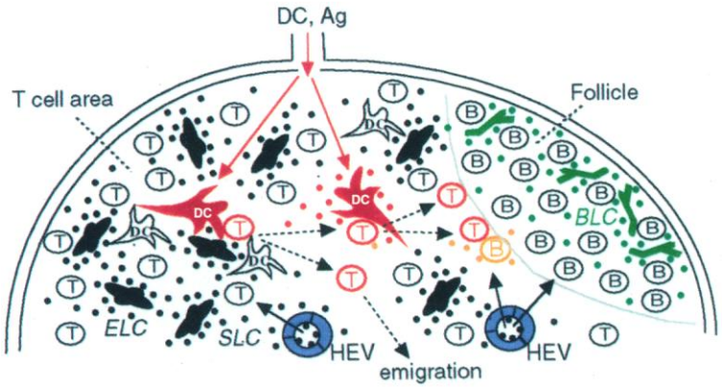

Fig. 3. Model of chemokine-directed movements in a lymph node early during the immune response. Naïve lymphocytes (outlined in black) migrate into the lymphoid tissue across SLC-producing HEVs (shaded blue), and SLC and ELC (black dots), and BLC (green dots) help guide cells to T and B cell areas, respectively. SLC- and ELC-producing cells in the T cell area are shaded black; BLC-producing cells in the B cell area (follicle) are shaded green. Maturing dendritic cells (DCs) bearing antigen (shaded red) migrate from afferent lymphatics into the T cell area in response to SLC and ELC. A naïve T cell recognizes the antigen and becomes activated (red outline) and divides. Activated T cells may then migrate more efficiently than the surrounding naïve T cells toward other newly arriving DCs that are expressing attractants of activated T cells (for example, MDC, red dots). Some activated T cells may decrease CCR7 and up-regulate CXCR5 and become directed toward the follicles. Naïve B cells that have bound antigen (shown in orange) move to the boundary of B and T zones and possibly secrete chemokines (orange dots) that help recruit activated helper T cells. Other activated T cells (helper and cytotoxic) exit the lymph node and travel to the inflamed site to function as effector cells.

Changes also occur in the tropism of T cells during their activation in the T cell zone that may enhance their intrinsic propensity to migrate to the B cell area (*32*). Under immunization conditions that promote strong stimulation of DCs, many antigen-specific T cells are induced to up-regulate expression of CXCR5 and to become responsive to BLC, while at the same time becoming less responsive to SLC and ELC (*34*). CXCR5 up-regulation on T cells depends on signaling via CD28 and may be strongly promoted by engagement of OX40 (*35*). T_H2 cells generated under certain in vitro conditions also have greatly reduced responsiveness to SLC and ELC, a result of decreased CCR7 expression, although they may not express CXCR5 (*36*). After adoptive transfer, these T_H2 cells but not T_H1 cells migrate to the edge of B cell areas in spleen (*36*). Together these findings suggest a model where reduced responsiveness to SLC and ELC causes a T cell to become excluded from the central T cell area. As a result of this exclusion, the cell may enter the gradient of chemokine emanating from antigen-engaged B cells, as well as the BLC coming from follicles. The possible significance of these movements in helping rare antigen-specific T cells to find rare antigen-presenting B cells is supported by the reduced ability of T_H2 cells to help the antibody response when they are redirected into the central T cell area by enforced expression of CCR7 (*36*). In the small number of studies performed in CXCR5-deficient mice and in mice lacking MIP-1α or CCR5, a MIP-1α and β receptor (Table 1), however, antibody responses have been in the normal range (*13, 37*), indicating that these molecules may not be critical for T and B cells to interact. Further experiments are needed that test the response to various pathogens and to low doses of antigen, both in these mice and in other gene-targeted animals, before the contribution of the various chemokines and receptors to the efficiency of T-B interactions is understood. How cells subsequently organize into a germinal center, and how plasma cells migrate to medullary cords, splenic red pulp, or bone marrow sinuses remains unclear but seems certain to involve further chemokines.

Effector and memory T cells. While events take place in the lymphoid organ, activated T cells begin returning to circulation to migrate to the site of infection and to function as cytokine-releasing effector cells or cytolytic cells. The factors regulating cell exit from lymphoid organs are unclear. A possible role for chemokines in determining retention time in the organ is supported by the recent evidence that stromal cell–derived factor SDF-1 functions in B cell and granulocyte development, at least in part, by promoting precursor cell retention in fetal liver and bone marrow (*38*). Migration from circulation into an inflamed tissue, like entry to lymphoid organs, involves selectin ligands, integrins, and chemokine receptors; differential expression of each of these classes of molecules imparts specificity to effector T cell trafficking (*6*). Activated T cells express receptors for many inflammatory chemokines (*2, 5*). As already discussed, there are differences in receptor expression between cells of T_H1 and T_H2 phenotype, and these may help direct the cells to distinct types of inflamed tissue (*27*). However, chemokine receptor expression tends not to correlate strictly with the T_H1 and T_H2 cytokine profile of T cells (*27*), and it seems likely that additional factors influence the pattern of receptor expression. Perhaps cells activated in different lymphoid organs come to express chemokine receptors that help them migrate to tissues drained by the particular organ. Consistent with this possibility, the CCR4 ligand, TARC, is preferentially expressed at sites of cutaneous inflammation, and cutaneous memory T cells, but not intestinal memory T cells, express CCR4 (*39*). In addition to expression of receptors for inflammatory chemokines, memory T cells have reduced expression of CCR7 compared with naïve cells (*40*), and this may contribute to their reduced trafficking through lymph nodes (*6*). However, when stimulated by antigen they can quickly reacquire SLC and ELC responsiveness (*40*). This should help ensure that, when small numbers of memory cells become activated at a site of infection, they can migrate into SLC-producing lymphatic vessels and travel, along with antigen-carrying DCs, into the SLC- and ELC-producing T cell area of the draining lymph node. Because maturing DCs produce chemokines that can attract activated T cells (*21, 26*), the activated memory cells are likely to move quickly into contact with antigen-bearing DCs, making for a rapid start to the secondary immune response.

Future Perspectives

Investigations are only at a beginning, and it is already apparent that lymphoid organs contain an immensely complex chemokine landscape. A cell is likely to be exposed to several chemokine gradients as it moves. Elegant in vitro studies have provided insight into how neutrophils that move up one chemokine gradient can, upon entering into the field of a second, turn and migrate up the new gradient (*41*). It will be exciting to see how many turns a lymphocyte can make as it travels through the multiple chemokine gradients in a lymphoid organ. Several classes of molecules are known that regulate G protein–coupled receptor signaling, including kinases, arrestins, and regulator of G protein–signaling (RGS) molecules, and their involvement in regulating chemokine responsiveness has only just begun to be addressed (*42*). These molecules are likely to play a part in the mechanism by which signals from other receptors, such as antigen receptors, are able to modify chemokine responsiveness of cells. Antigen-receptor signaling regulates the migration of cells that bind autoantigen, as well as those that bind foreign antigen, and an area of continuing investigation is determining the role chemokines play in helping maintain immunological self-tolerance (*31*). Ongoing studies also seem destined to uncover an expanding role for chemokines in development. This not only includes critical roles in positioning cells in appropriate subcompartments of fetal liver, bone marrow, and thymus for lineage development (*2*), but also roles in organ development. The lack of inguinal lymph nodes in CXCR5-deficient mice (*13*) provides the first example of what is likely to be a larger role in lymphoid organ development, as there is evidence that recruitment of specialized migratory cells is essential for the development of all lymph nodes and Peyer's patches (*43*). A broader role in development is also suggested by the brain, heart, and vascular defects in SDF-1–and CXCR4-deficient mice (*44*). A long-standing and fundamental problem in developmental biology has been understanding over what distance a morphogen can act (*45*), and it will be a similarly important challenge for immunologists to determine the distances over which chemokines act and to understand whether a chemokine can, in fact, act like a morphogen and induce different properties in a cell, depending on its position in the gradient. Morphogen activity is negatively regulated by secreted factors, and these help establish pattern in the developing organism (*45*). Proteoglycans and proteases can regulate chemokine activity, and several viral chemokine inhibitors exist for which host orthologs are still to be found (*46*). It is going to be interesting to see how these and other molecules operate to regulate the activity of chemokines and help to establish, maintain, and modify the pattern of cell migration in lymphoid organs.

References and Notes

1. P. D. McMaster and S. S. Hudack, *J. Exp. Med.* **51**, 783 (1935); J. L. Gowans and E. J. Knight, *Proc. R. Soc. London Ser. B* **159**, 257 (1964).
2. A. Zlotnik, J. Morales, J. A. Hedrick, *Crit. Rev. Immunol.* **19**, 1 (1999); M. Baggiolini, *Nature* **392**, 565 (1998); B. Dixon *et al.*, *Immunol. Rev.* **166**, 341 (1998); O. Yoshie, T. Imai, H. Nomiyama, *J. Leukocyte Biol.* **62**, 634 (1997).
3. M. Tessier-Lavigne and C. S. Goodman, *Science* **274**, 1123 (1996).
4. O. D. Weiner, G. Servant, C. A. Parent, P. N. Devreotes, H. R. Bourne, in *Cell Polarity: Frontiers in Molecular Biology*, D. G. Drubin, Ed. (Oxford Univ. Press, Oxford, 1999).
5. J. J. Oppenheim, C. O. C. Zachariae, J. Mukaida, K. Matsushima, *Annu. Rev. Immunol.* **9**, 617 (1991); T. J. Schall and K. B. Bacon, *Curr. Opin. Immunol.* **6**, 865 (1994); M. Baggiolini, B. Dewald, B. Moser, *Adv. Immunol.* **55**, 97 (1994).
6. E. C. Butcher and L. J. Picker, *Science* **272**, 60 (1996); T. A. Springer, *Cell* **76**, 301 (1994).

7. G. J. Spangrude, B. A. Braaten, R. A. Daynes, *J. Immunol.* **132**, 354 (1984).
8. M. Nagira *et al.*, *J. Biol. Chem.* **272**, 19518 (1997); J. A. Hedrick and A. Zlotnik, *J. Immunol.* **159**, 1589 (1997); R. Hromas *et al.*, *J. Immunol.* **159**, 2554 (1997); M. D. Gunn *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 258 (1998); K. Williman *et al.*, *Eur. J. Immunol.* **28**, 2025; M. Nagira *et al.*, *Eur. J. Immunol.* **28**, 1516 (1998).
9. J. J. Campbell *et al.*, *Science* **279**, 381 (1998); K. Tangemann, M. D. Gunn, P. Giblin, S. D. Rosen, *J. Immunol.* **161**, 6330 (1998).
10. M. D. Gunn, *et al.*, *J. Exp. Med.* **189**, 451 (1999); H. Nakano, *et al.*, *Blood* **91**, 2886 (1998).
11. R. Yoshida *et al.*, *J. Biol. Chem.* **273**, 7118 (1998).
12. R. Förster *et al.*, *Cell* **99**, 23 (1999).
13. R. Förster, T. Emrich, E. Kremmer, M. Lipp, *Blood* **84**, 830 (1994); R. Förster *et al.*, *Cell* **87**, 1037 (1996).
14. M. D. Gunn *et al.*, *Nature* **391**, 799 (1998); D. F. Legler *et al.*, *J. Exp. Med.* **187**, 655 (1998).
15. Y.-X. Fu and D. D. Chaplin, *Annu. Rev. Immunol.* **17**, 399 (1999).
16. V. N. Ngo *et al.*, *J. Exp. Med.* **189**, 403 (1999).
17. S. Tanabe *et al.*, *J. Immunol.* **159**, 5671 (1997).
18. R. Yoshida *et al.*, *J. Biol. Chem.* **272**, 13803 (1997); D. L. Rossi *et al.*, *J. Immunol.* **158**, 1033 (1997); V. N. Ngo, H. L. Tang, J. G. Cyster, *J. Exp. Med.* **188**, 181 (1998); C. H. Kim *et al.*, *J. Immunol.* **160**, 2418 (1998).
19. T. J. Reape *et al.*, *Am. J. Pathol.* **154**, 365 (1999); R. Yoshida *et al.*, *Int. Immunol.* **10**, 901 (1998); M.-C. Dieu *et al.*, *J. Exp. Med.* **188**, 373 (1998); F. Sallusto, *et al.*, *Eur. J. Immunol.* **28**, 2760 (1998).
20. J. Banchereau and R. M. Steinman, *Nature* **392**, 245 (1998); K. Shortman and C. Caux, *Stem Cells* **15**, 409 (1997); J. G. Cyster, *J. Exp. Med.* **189**, 447 (1999).
21. F. Sallusto *et al.*, *Eur. J. Immunol.* **29**, 1617 (1999); M. Foti *et al.*, *Int. Immunol.* **11**, 979 (1999).
22. H. Saeki, A. M. Moore, M. J. Brown, S. T. Hwang, *J. Immunol.* **162**, 2472 (1999).
23. S. A. Kellermann, S. Hudak, E. R. Oldham, Y. J. Liu, L. M. McEvoy, *J. Immunol.* **162**, 3859 (1999); V. W. F. Chan *et al.*, *Blood* **93**, 3610 (1999).
24. G. J. Adema *et al.*, *Nature* **387**, 713 (1997); V. Kodelja *et al.*, *J. Immunol.* **160**, 1411 (1998); P. Guan *et al.*, *Genomics* **56**, 296 (1999).
25. A. A. Freitas and B. Rocha, *Curr. Opin. Immunol.* **11**, 152 (1999).
26. H. L. Tang and J. G. Cyster, *Science* **284**, 819 (1999).
27. A. O'Garra, L. M. McEvoy, A. Zlotnik, *Curr. Biol.* **8**, R646 (1998).
28. E. Papadopoulos *et al.*, *Eur. J. Immunol.* **29**, 2551 (1999); T. Imai *et al.*, *Cell* **91**, 521 (1997).
29. J. E. Gretz, A. O. Anderson, S. Shaw, *Immunol. Rev.* **156**, 11 (1997); J. G. Tew *et al.*, *Immunol. Rev.* **156**, 39 (1997).
30. Y.-J. Liu, J. Zhang, P. J. L. Lane, E. Y.-T. Chan, I. C. M. Maclennan, *Eur. J. Immunol.* **21**, 2951 (1991); J. Jacob, R. Kassir, G. Kelsoe, *J. Exp. Med.* **173**, 1165 (1991).
31. J. G. Cyster, S. B. Hartley, C. C. Goodnow, *Nature* **371**, 389 (1994); J. G. Cyster, *Immunol. Rev.* **156**, 87 (1997).
32. P. Garside *et al.*, *Science* **281**, 96 (1998).
33. C. Schaniel *et al.*, *J. Exp. Med.* **188**, 451 (1998); R. Krzysiek *et al.*, *J. Immunol.* **162**, 4455 (1999).
34. K. M. Ansel, L. J. McHeyzer-Williams, V. N. Ngo, M. G. McHeyzer-Williams, J. G. Cyster, *J. Exp. Med.* **190**, 1123 (1999).
35. S. Flynn, K. M. Toellner, C. Raykundalia, M. Goodall, P. Lane, *J. Exp. Med.* **188**, 297 (1998); T. Brocker *et al.*, *Eur. J. Immunol.* **29**, 1610 (1999).
36. D. A. Randolph, G. Huang, C. J. L. Carruthers, L. E. Bromley, D. D. Chaplin, *Science* **286**, 2159 (1999).
37. D. N. Cook *et al.*, *Science* **269**, 1583 (1995); Y. Zhou *et al.*, *J. Immunol.* **160**, 4018 (1998).
38. Q. Ma, D. Jones, T. A. Springer, *Immunity* **10**, 463 (1999); T. Nagasawa *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 14726 (1996).
39. J. J. Campbell *et al.*, *Nature* **400**, 776 (1999).
40. F. Sallusto *et al.*, *Eur. J. Immunol.* **29**, 2037 (1999).
41. E. F. Foxman, J. J. Campbell, E. C. Butcher, *J. Cell Biol.* **139**, 1349 (1997).
42. E. P. Bowman *et al.*, *J. Biol. Chem.* **273**, 28040 (1998); R. Guinamard *et al.*, *J. Exp. Med.* **189**, 1461 (1999); H. Ali, R. M. Richardson, B. Haribabu, R. Snyderman, *J. Biol. Chem.* **274**, 6027 (1999).
43. Y. Yokota *et al.*, *Nature* **397**, 702 (1999).
44. Y. R. Zou, A. H. Kottmann, M. Kuroda, I. Taniuchi, D. R. Littman, *Nature* **393**, 595 (1998); K. Tachibana *et al.*, *Nature* **393**, 591 (1998); Q. Ma *et al.*, *Proc. Natl. Acad. Sci. U. S. A.* **95**, 9448 (1998).
45. C. Neumann and S. Cohen, *Bioessays* **19**, 721 (1997).
46. T. N. Kledal *et al.*, *Science* **277**, 1656 (1997); A. Alcamí, J. A. Symons, P. D. Collins, T. J. Williams, G. L. Smith, *J. Immunol.* **160**, 624 (1998); P. Proost *et al.*, *J. Biol. Chem.* **273**, 7222 (1998); A. J. Hoogewerf *et al.*, *Biochemistry* **36**, 13570 (1997).

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References and Notes

[3] **The Molecular Biology of Axon Guidance**
Marc Tessier-Lavigne; Corey S. Goodman
Science, New Series, Vol. 274, No. 5290. (Nov. 15, 1996), pp. 1123-1133.
Stable URL:
http://links.jstor.org/sici?sici=0036-8075%2819961115%293%3A274%3A5290%3C1123%3ATMBOAG%3E2.0.CO%3B2-1

[6] **Lymphocyte Homing and Homeostasis**
Eugene C. Butcher; Louis J. Picker
Science, New Series, Vol. 272, No. 5258. (Apr. 5, 1996), pp. 60-66.
Stable URL:
http://links.jstor.org/sici?sici=0036-8075%2819960405%293%3A272%3A5258%3C60%3ALHAH%3E2.0.CO%3B2-A

[8] **A Chemokine Expressed in Lymphoid High Endothelial Venules Promotes the Adhesion and Chemotaxis of Naive T Lymphocytes**
Michael D. Gunn; Kirsten Tangemann; Carmen Tam; Jason G. Cyster; Steven D. Rosen; Lewis T. Williams
Proceedings of the National Academy of Sciences of the United States of America, Vol. 95, No. 1. (Jan. 6, 1998), pp. 258-263.
Stable URL:
http://links.jstor.org/sici?sici=0027-8424%2819980106%2995%3A1%3C258%3AACEILH%3E2.0.CO%3B2-C

LINKED CITATIONS

[9] **Chemokines and the Arrest of Lymphocytes Rolling Under Flow Conditions**

James J. Campbell; Joseph Hedrick; Albert Zlotnik; Michael A. Siani; Darren A. Thompson; Eugene C. Butcher

Science, New Series, Vol. 279, No. 5349. (Jan. 16, 1998), pp. 381-384.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819980116%293%3A279%3A5349%3C381%3ACATAOL%3E2.0.CO%3B2-E

[26] **Chemokine Up-Regulation and Activated T Cell Attraction by Maturing Dendritic Cells**

H. Lucy Tang; Jason G. Cyster

Science, New Series, Vol. 284, No. 5415. (Apr. 30, 1999), pp. 819-822.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819990430%293%3A284%3A5415%3C819%3ACUAATC%3E2.0.CO%3B2-X

[32] **Visualization of Specific B and T Lymphocyte Interactions in the Lymph Node**

Paul Garside; Elizabeth Ingulli; Rebecca R. Merica; Julia G. Johnson; Randolph J. Noelle; Marc K. Jenkins

Science, New Series, Vol. 281, No. 5373. (Jul. 3, 1998), pp. 96-99.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819980703%293%3A281%3A5373%3C96%3AVOSBAT%3E2.0.CO%3B2-K

[36] **The Role of CCR7 in T_H1 and T_H2 Cell Localization and Delivery of B Cell Help in Vivo**

David A. Randolph; Guangming Huang; Cynthia J. L. Carruthers; Lindsay E. Bromley; David D. Chaplin

Science, New Series, Vol. 286, No. 5447. (Dec. 10, 1999), pp. 2159-2162.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819991210%293%3A286%3A5447%3C2159%3ATROCIT%3E2.0.CO%3B2-T

[37] **Requirement of MIP-1# for an Inflammatory Response to Viral Infection**

Donald N. Cook; Melinda A. Beck; Thomas M. Coffman; Suzanne L. Kirby; John F. Sheridan; Ian B. Pragnell; Oliver Smithies

Science, New Series, Vol. 269, No. 5230. (Sep. 15, 1995), pp. 1583-1585.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819950915%293%3A269%3A5230%3C1583%3AROMFAI%3E2.0.CO%3B2-M

LINKED CITATIONS

[38] **Molecular Cloning and Characterization of a Murine Pre-B-Cell Growth-Stimulating Factor/Stromal Cell-Derived Factor 1 Receptor, a Murine Homolog of the Human Immunodeficiency Virus 1 Entry Coreceptor Fusin**

Takashi Nagasawa; Toshihiro Nakajima; Kazunobu Tachibana; Hisashi Iizasa; Conrad C. Bleul; Osamu Yoshie; Kouji Matsushima; Nobuaki Yoshida; Timothy A. Springer; Tadamitsu Kishimoto

Proceedings of the National Academy of Sciences of the United States of America, Vol. 93, No. 25. (Dec. 10, 1996), pp. 14726-14729.

Stable URL:

http://links.jstor.org/sici?sici=0027-8424%2819961210%2993%3A25%3C14726%3AMCACOA%3E2.0.CO%3B2-6

[44] **Impaired B-Lymphopoiesis, Myelopoiesis, and Derailed Cerebellar Neuron Migration in CXCR4- and SDF-1-Deficient Mice**

Qing Ma; Dan Jones; Paul R. Borghesani; Rosalind A. Segal; Takashi Nagasawa; Tadamitsu Kishimoto; Roderick T. Bronson; Timothy A. Springer

Proceedings of the National Academy of Sciences of the United States of America, Vol. 95, No. 16. (Aug. 4, 1998), pp. 9448-9453.

Stable URL:

http://links.jstor.org/sici?sici=0027-8424%2819980804%2995%3A16%3C9448%3AIBMADC%3E2.0.CO%3B2-M

[46] **A Broad-Spectrum Chemokine Antagonist Encoded by Kaposi's Sarcoma- Associated Herpesvirus**

Thomas N. Kledal; Mette M. Rosenkilde; Florence Coulin; Graham Simmons; Anders H. Johnsen; Sami Alouani; Christine A. Power; Hans R. Lüttichau; Jan Gerstoft; Paul R. Clapham; Ian Clark-Lewis; Timothy N. C. Wells; Thue W. Schwartz

Science, New Series, Vol. 277, No. 5332. (Sep. 12, 1997), pp. 1656-1659.

Stable URL:

http://links.jstor.org/sici?sici=0036-8075%2819970912%293%3A277%3A5332%3C1656%3AABCAEB%3E2.0.CO%3B2-5