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Lymphocyte Homing and Homeostasis

Eugene C. Butcher and Louis J. Picker

The integration and control of systemic immune responses depends on the regulated trafficking of lymphocytes. This lymphocyte "homing" process disperses the immunologic repertoire, directs lymphocyte subsets to the specialized microenvironments that control their differentiation and regulate their survival, and targets immune effector cells to sites of antigenic or microbial invasion. Recent advances reveal that the exquisite specificity of lymphocyte homing is determined by combinatorial "decision processes" involving multistep sequential engagement of adhesion and signaling receptors. These homing-related interactions are seamlessly integrated into the overall interaction of the lymphocyte with its environment and participate directly in the control of lymphocyte function, life-span, and population dynamics. In this article a review of the molecular basis of lymphocyte homing is presented, and mechanisms by which homing physiology regulates the homeostasis of immunologic resources are proposed.

The immune system faces daunting challenges in its mission of protecting the body from microbial invasion. From a large but finite number of antigen-receptor–defined lymphocyte clones, it must establish and maintain a diverse, nonautoimmune population of mature lymphocytes and endow them with the capability to respond to foreign antigen wherever it may enter the body. It must control the interplay between B cells, T cells, specialized accessory cell populations, and antigen so as to efficiently initiate primary cellular and humoral immune responses. It must integrate immune responses throughout the body, while at the same time targeting and permitting specialization of immune response modalities in different regions of the body such as the alimentary tract, the lung, and the skin. Finally, the immune system must use efficient mechanisms of homeostasis to provide for long-lasting but malleable immunity over time and to prevent the overexpansion or depletion of specialized lymphocyte subsets. To accomplish these diverse tasks, evolution has created a dispersed system of highly specialized immune microenvironments that control the differentiation and homeostasis of mature lymphocytes and then linked these microenvironments together with each other and with the effector sites of the body through an elaborate system of lymphocyte homing and recirculation.

Our purpose in this review is to describe recent molecular and conceptual advances in our understanding of lymphocyte recirculation and homing; to emphasize the importance of targeted lymphocyte migration in the integration, regulation, and specialization of immune responses; and to explore emerging concepts of the role of recirculation and microenvironmental homing in immune homeostasis.

Lymphocyte Recirculation and Homing from the Blood

Most mature lymphocytes recirculate continuously, going from blood to tissue and back to blood again as often as one to two times per day (*1*). Recirculation is not random, but rather is targeted by active mechanisms of lymphocyte–endothelial cell rec-

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ognition (2) that, along with the subsequent diapedesis of the lymphocytes across the vascular wall, direct lymphocyte homing from the blood (3–5). This process of extravasation is a critical regulatory point in the immune system, controlling the access of specialized lymphocyte subsets to particular tissues and thus influencing the nature of local immune and inflammatory responses. Its specificity depends on developmental, tissue- and inflammation-specific specialization of vascular phenotypes and on developmental and microenvironmental regulation of lymphocyte homing and chemoattractant receptors (3–7).

Perhaps the most significant dichotomy in lymphocyte trafficking concerns the differential distribution of naïve versus memory/effector populations (Fig. 1) (3, 5, 8, 9). In general, naïve lymphocytes are programmed to recirculate through secondary lymphoid tissues (lymph nodes, Peyer's patches, tonsils, and spleen). These organs collect antigen from epithelial surfaces, somatic tissues, and blood and present it to naïve B and T cells in the context of specialized lymphoid microenvironments that can drive their antigen-induced differentiation while at the same time culling autoreactive cells. Most memory and effector lymphocytes probably traffic through lymphoid organs as well, but unlike naïve cells, they can also access and recirculate through extralymphoid immune effector sites (for example, intestinal lamina propria, pulmonary interstitium, inflamed skin, and joints). Moreover, whereas the homing behavior of naïve cells is relatively homogenous within a class [for example B cell versus T cell (3, 8)], the homing behavior of memory and effector lymphocytes is extremely heterogeneous, with distinct subsets displaying restricted, often tissue-selective patterns of recirculation (3, 5, 8, 9). Tissue-selective homing targets memory cells and immunoblasts to sites where they are most likely to encounter (or reencounter) their specific antigen or are best adapted to function, and permits the segregation and specialization of immune responses in different regions of the body (for example, mucosal versus nonmucosal tissues). One example of such tissue-selective homing of "site"-specialized effector cells is the targeted migration of plasmablasts expressing immunoglobulin A (IgA) to mucosal surfaces of the body [reviewed in (3)].

Implicit in the differential trafficking of naïve and memory cells is the concept that homing behavior, like other specific lymphocyte functions, can be repeatedly regulated during the life-span of the lymphocyte, particularly during antigen-induced differentiation processes such as the naïve to memory/effector transition (3, 10) (but perhaps also, in certain instances, without such activation). Under the influence of local microenvironments supporting antigen-induced activation, responding lymphocyte populations may increase or decrease expression of existing homing receptors (for example, L-selectin and $\alpha_4\beta_7$ integrin, see Table 1) or up-regulate new homing receptors (for example, the skin-homing receptor) (11–13). These responding lymphocyte populations may also be able to alter the functional status or activatibility of activation-dependent adhesion molecules such as the various integrins (11, 13). Homing receptor regulation during memory/effector T cell differentiation is analogous to (and temporally concomitant with) that of effector cytokine production [for example, interferon γ, interleukin-2 (IL-2), IL-4, and the T helper cell type 1 (T_H1) versus T_H2 subsets], involving immunoregulatory cytokines as well as the nature of antigenic and costimulatory signals (10).

Molecular Regulation of Lymphocyte Extravasation

Evolution has confronted the physical challenge of high intravascular shear forces [up to ~30 dynes/cm^2 in postcapillary venules mediating lymphocyte extravasation (14)] and the requirement for targeted leukocyte trafficking by making extravasation a multistep process in which initial interaction under flow conditions and subsequent stabilization of binding can be mediated by independent, specialized adhesion pathways (15–18). The recruitment process has been separated into four successive steps: (i) primary adhesion, which is transient and reversible in seconds; (ii) rapid (seconds) lymphocyte "activation"; (iii) activation-

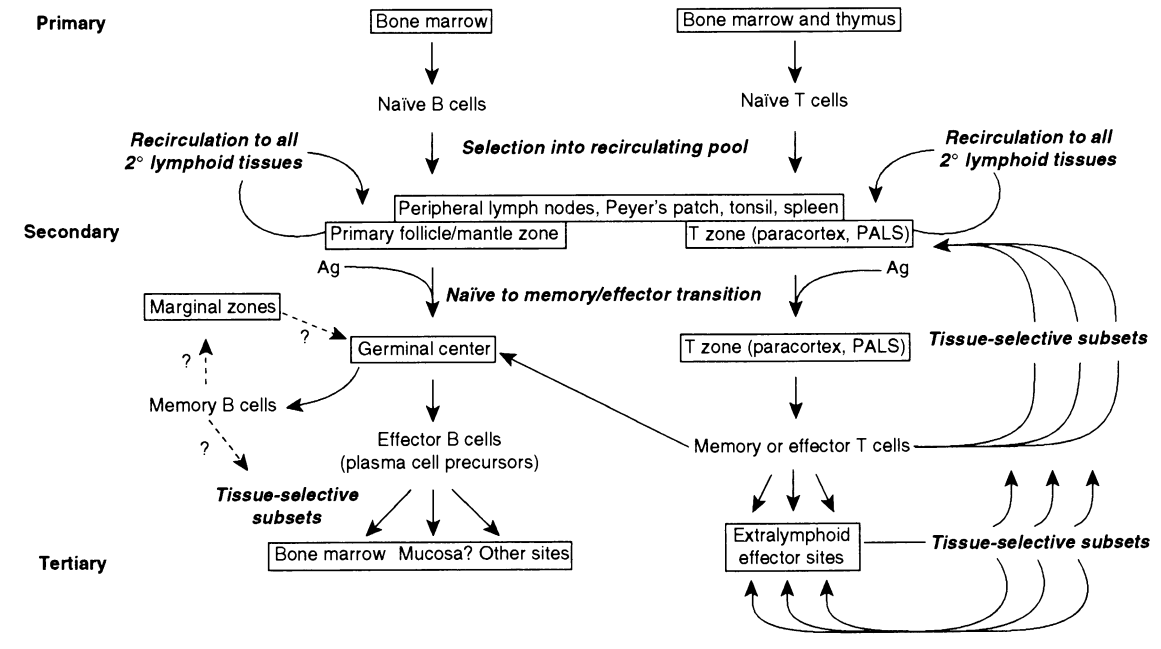

Fig. 1. Naïve lymphocytes home to specific microenvironments within secondary lymphoid tissues and recirculate through these sites until they either die or encounter their specific antigen. Unlike naïve cells, memory and effector T (and probably B) cells can efficiently extravasate in tertiary (extralymphoid) inflammatory sites, with subsets displaying targeted trafficking through, for example, inflamed skin, intestinal mucosa, pulmonary tissues, and joints. Antigen-activated B cells may home to specialized environments in the outer T zone during primary responses, or may colonize germinal center sites of hypermutation, affinity maturation, and memory cell differentiation. Less abundant, specialized lymphocyte subsets include γδ T cells in the mouse, and subsets of gut intraepithelial leukocytes, that may be targeted directly from their origin in the thymus or bone marrow to reproductive, cutaneous, intestinal, or other tertiary tissues (not illustrated). The extralymphoid effector sites of selective homing include (at least) skin, lung, intestinal lamina propria, and synovium. PALS, periarteriolar lymphoid sheath; Ag, antigen.

dependent "arrest" that is stable under shear forces but potentially reversible over minutes; and (iv) diapedesis (Fig. 2). Lymphocyte recruitment is thus controlled by an algorithm involving a series of "yes" (continue to the next step) or "no" (return to the blood) decisions. Homing can be regulated at any or all of the decision points, and the implications of this for combinatorial diversity, specificity, and mechanistic resiliency in leukocyte trafficking have been discussed in detail (*15*). Table 1 lists some key molecular players identified to date, each involved in their own distinct, if overlapping, settings of physiologic lymphocyte homing. The molecular biology of these molecules has been reviewed in the context of leukocyte trafficking (*17–21*). Here, we will focus on recent advances in our molecular understanding of lymphocyte extravasation, especially on unifying functional features that determine the specialized roles of adhesion and signaling receptors in the multistep process, and on the ability of these receptors to cooperate physiologically to create specific homing pathways.

In the first step (Fig. 2, steps 1a and 1b), constitutively functional lymphocyte receptors interact with their regulated vascular ligands under high flow conditions. This primary adhesion can involve separable contact formation ("tethering") with loose rolling of the lymphocyte along the vessel wall, and molecularly distinct mechanisms for slowing the rolling velocity (*17, 22, 23*). In other situations, it can involve a transient, immediate arrest without discernible rolling (*22, 23*). This primary adhesion slows the transit of lymphocytes, thus allowing sufficient time for the lymphocyte to sample the vessel for soluble or endothelial surface proadhesive factors. The remarkable specialization of primary homing receptors is illustrated by L-selectin, a C-type lectin with an affinity for sulfated, fucosylated carbohydrate determinants displayed by specialized postcapillary venules, especially the high endothelial venules (HEV) in lymph nodes where these carbohydrate ligands are presented by a number of glycoproteins composing the peripheral lymph node addressin (PNAd) (*24*). Strikingly, L-selectin is highly concentrated on the tips of lymphocyte microvilli (the sites of initial cell-cell contact under flow), a feature it shares with other tethering receptors (for example, the α_4 integrins and probably PSGL-1) and which dramatically enhances the efficiency of receptor engagement under physiologic shear forces (*25*). In fact, efficient interaction through L-selectin actually appears to require cell motion (*26*). Finally, reversibility of L-selectin interaction is further ensured by a proteolytic mechanism that rapidly cleaves L-selectin near the cell membrane upon cross-linking (*27*), so that even if multivalent L-selectin interactions should mediate arrest, cells would be spontaneously released in the absence of reinforcing mechanisms. Thus, the topographic and molecular specialization of L-selectin simultaneously permits efficient interactions of blood lymphocytes under flow conditions, prevents inappropriate interactions during vascular stasis, and ensures the reversibility of primary adhesion in the absence of subsequent events in the multistep process.

Subsets of lymphocytes can also attach and roll on vascular E- and P-selectins; on VCAM-1 and MAdCAM-1, Ig family vascular ligands for the microvillous-associated homing receptors $\alpha_4\beta_1$ and $\alpha_4\beta_7$; and probably on vascular adhesion protein–1 (VAP-1) (*17, 18, 23, 28–30*). Long-term (more than 6 hours) activated lymphocytes can also roll on endothelial hyaluronate by means of CD44 (*31*). Interestingly, physiologic studies confirm that α_4 integrins, unlike the selectins, can participate in both primary and secondary lymphocyte interactions with endothelium (*22, 29*). Characteristically, α_4 integrins also mediate much slower rolling than L-selectin, an important distinction as in some situations they (or other molecules) can be required as a "bridge" to slow selectin-initiated rolling sufficiently for engagement of activation-dependent adhesion mechanisms (see below).

Although in situ studies demonstrate involvement of an "activation" step in the lymphocyte extravasation process (Fig. 2, step 2), the physiologic "triggers" for this

Table 1. Adhesion molecules involved in lymphocyte-endothelial recognition. Abbreviations: CHO, carbohydrate; PNAd, peripheral lymph node addressin; MAdCAM, mucosal addressin cell adhesion molecule; HEV, high endothelial venule; CLA, cutaneous lymphocyte-associated antigen; PSGL, P-selectin glycoprotein ligand; VCAM, vascular cell adhesion molecule; LFA, leukocyte function antigen; ICAM, intracellular adhesion molecule; HCAM, hyaluronate-binding cell adhesion molecule; and VAP, vascular adhesion protein. Primary adhesion involves steps 1a and 1b of Fig. 2 and secondary adhesion is step 3.

Lymphocyte homing receptor	Predominant endothelial cell ligands	Role in multistep extravasation	Primary homing pathways
Selectin-CHO			
L-selectin (CD62L)	PNAd (includes CD34, other protein cores)	1° adhesion	Naïve lymphocyte homing to lymph nodes; lymphocyte homing to peripheral > mucosal sites of severe chronic inflammation (*5, 10*)
	MAdCAM-1 (HEV-selective sulfated CHO modification of mucin domain)	1° (step 1a only)	Naïve lymphocyte homing to Peyer's patches (*22*)
CLA	E-selectin	1° adhesion	Memory T cell homing to skin (*10*)
o-Linked glycans and sulfate probably associated with PSGL-1	P-selectin	1° adhesion	? (*28*)
Integrin-Ig family			
$\alpha_4\beta_7$	MAdCAM-1 (mucosal addressin)	1° and 2° adhesion	Naïve lymphocyte homing to Peyer's patch and appendix; memory lymphocyte homing to nonpulmonary mucosal sites (*22, 29*)
$\alpha_4\beta_1$	VCAM-1	1° and 2° adhesion	Memory lymphocyte (blast) homing to many extra-intestinal inflammatory sites (*17*)
$\alpha_L\beta_2$ (LFA-1)	ICAM-1, -2, ?others	2° adhesion	Widespread involvement
Other			
CD44 (HCAM)	Hyaluronate	1° adhesion	? Homing of activated lymphocytes (blasts) to inflammatory sites (*31*)
?	VAP-1	1° adhesion	? Unknown subset homing to (?inflamed) HEV in human, lymph nodes, tonsils, and sites of inflammation (*30*)

activation remain to be defined for lymphocytes. Integrin activation can occur during in situ lymphocyte-endothelial interactions as rapidly as 1 to 3 s after contact, and it is clear that (at least in the cases examined so far) triggering of integrin-dependent arrest involves pertussis toxin–sensitive $G\alpha_i$ protein–linked receptors (*32*), presumably of the seven-transmembrane or serpentine chemoattractant family. These receptors, when expressed at high levels [for example on neutrophils, but also on chemoattractant receptor-transfected lymphocytes (*33*)], can trigger integrin adhesion to vascular ligands in seconds through an intracellular signaling pathway involving the small guanosine triphosphate (GTP)–binding protein Rho (*33, 34*); moreover, such integrin activation reverses spontaneously in minutes, which would allow cells arrested in vivo to revert to rolling in the absence of signals leading to diapedesis. Initial excitement about the involvement of the chemokine family of chemoattractants in step 2 has been dampened by the finding that most resting lymphocytes express only low levels of known chemokine receptors (*7, 35*) and appear incapable of sufficiently robust proadhesive responses to these agents to account for rapid intravascular arrest (*7, 36*). As yet undiscovered chemokine or other serpentine receptors may be involved, although participation of other receptor classes cannot be excluded. Importantly, step 2 activation signals may not be required for arrest of circulating immunoblasts expressing preactivated integrins (*22*).

To date only the heterodimeric integrins, including the α_4 integrins $\alpha_4\beta_1$ and $\alpha_4\beta_7$ and the β_2 integrins LFA-1 ($\alpha_L\beta_2$) and MAC-1 ($\alpha_M\beta_2$), have been implicated in the third step, activation-dependent stable arrest (Fig. 2). Interestingly, unlike the α_4 integrins, β_2 integrins are found on the planar cell body of leukocytes and are largely excluded from microvilli (*37*). This exclusion from sites of first cell contact may explain in part the inability of β_2 integrins, even when preactivated, to initiate lymphocyte adhesion under flow. In the presence of appropriate haptotactic or chemoattractant signals, activation-dependent stable arrest is followed by diapedesis, the final step in extravasation. The same β_2 and α_4 integrins involved in lymphocyte arrest on endothelium can also participate in transendothelial migration, probably in conjunction with other adhesion receptors (*17*).

Recent physiologic studies have confirmed the involvement of multimolecular cascades in lymphocyte-endothelial recognition and illustrate how, with relatively few adhesive interactions, these cascades can yield tissue-specific homing. For example, in situ studies of exteriorized mouse intestines (*22, 29*) have provided a paradigm for how naïve lymphocytes can be targeted to secondary lymphoid tissues (Peyer's patches), while memory/effector cells but not naïve cells are targeted to specific extralymphoid effector sites (intestinal lamina propria). The unique phenotypes of Peyer's patch HEV (L-selectin ligand^{lo}, MAdCAM-1^{hi}, ICAM-1$^+$, and ICAM-2$^+$) and, correspondingly, of naïve lymphocytes (L-selectin$^+$, $\alpha_4\beta_7^{lo\text{-}med}$, and LFA-1$^+$) conspire to make molecular cooperation essential for successful extravasation in this tissue: Efficient arrest of naïve cells requires the sequential engagement of L-selectin to initiate contact, $\alpha_4\beta_7$ to slow rolling, and LFA-1 in conjunction with $\alpha_4\beta_7$ to mediate activation-dependent arrest. L-selectin dominates contact initiation because naïve lymphocytes display only relatively low levels and activity of $\alpha_4\beta_7$. On the other hand, L-selectin rolling on Peyer's patch HEV (which express only low levels of L-selectin ligand) is too loose to allow direct engagement of LFA-1, thus necessitating "bridging" involvement of $\alpha_4\beta_7$. The additional requirement for LFA-1 for arrest may also reflect the low levels of $\alpha_4\beta_7$ on naïve cells. α_4 integrins are not required for naïve lymphocyte homing to peripheral lymph nodes (whose HEV lack MAdCAM-1), and in this site an alternative (unknown) bridging molecule may be involved, or because peripheral lymph node HEV display uniquely high levels of L-selectin ligands, L-selectin–mediated rolling may be slow enough to allow direct conversion to LFA-1–mediated arrest. Importantly, $\alpha_4\beta_7$ levels on naïve cells are insufficient to promote their direct binding to the MAdCAM-1$^+$, L-selectin ligand$^-$ venules in the intestinal lamina propria (an extralymphoid "effector" site) (*29*). These mechanisms thus ensure that naïve lymphocytes have access to both mucosal and peripheral secondary lymphoid tissues but not to mucosal effector sites. On the other hand, $\alpha_4\beta_7^{hi}$ cells (a model of mucosal memory lymphocytes and immunoblasts) can effectively interact with these lamina propria venules using $\alpha_4\beta_7$ alone (*29*). Thus, by varying the expression of highly specialized homing receptors and their endothelial counterreceptors, and by allowing their sequential cooperation in variations on the multistep theme, the immune system can construct many specific homing pathways using relatively few distinct molecular components (see also Fig. 3).

Molecular Regulation of Microenvironmental Homing

Once recruited into tissues, lymphocytes disperse into specialized microenvironmental domains. Examples include the B cell follicles and T cell zones of secondary lymphoid tissues and initial localization of antigen-reactive B cells to the outer T zone in primary immune responses and to the well-delineated germinal centers during memory cell formation (*38*) (Fig. 1). Lymphocyte subsets tend to segregate into discrete areas in extralymphoid tissues and sites of inflammation as well. In a general sense, however, microenvironments need not be geographically discrete; they can also be more dispersed, comprising scattered specialized stromal elements involved in lymphocyte homing and homeostasis. Just as mechanisms of tissue-selective trafficking permit segregation and specialization of immune responses at the systemic level, microenvironmental homing permits specialization of local stromal and accessory components (for example, the antigen-presenting follicular dendritic cells of B cell follicles and interdigitating cells of T cell zones) into domains capable of supporting the complex cellular interactions required for immune responses.

The molecular basis of microenviron-

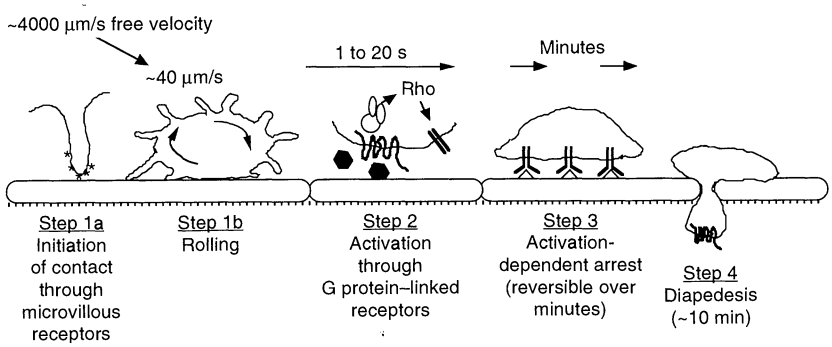

Fig. 2. The multistep model of lymphocyte–endothelial cell recognition and recruitment of lymphocytes from the blood. The potential requirement for four sequential independently regulated receptor-ligand interactions allows combinatorial determination of the specificity of lymphocyte homing (*15*), implying that the specificity of the overall process can greatly exceed that of its component steps. The mean velocities of free-flowing (noninteracting) and rolling lymphocytes from in situ microscopic observations of lymphocytes in Peyer's patch HEV are given (*22*); these values may differ in other vascular beds. G protein, heterotrimeric GTP-binding protein.

mental homing remains largely unexplored, but a number of conceptual and molecular themes deserve emphasis. First, homing within tissues, like recruitment from the blood, must be combinatorially determined by overlapping regulatory, adhesion, and migratory events (*39*). Each microenvironmental domain would be characterized by a unique, organized display of adhesive ligands and regulatory factors—both within the domain itself and leading to it from the microvasculature—such that lymphocyte migration can be targeted by sequential chemotactic or haptotactic and contact guidance mechanisms.

Second, as in the extravasation process, adhesion regulation is fundamental to the control of microenvironmental homing. In some instances, microenvironments may upregulate new lymphocyte adhesive elements such as the transforming growth factor–β1 (TGF-β1)–inducible $\alpha_e\beta_7$ integrin, which targets lymphocytes to intraepithelial sites by binding to E-cadherin (*40*). In other instances constitutively expressed adhesion molecules (including many of those associated with extravasation) may be involved; for example, α_4 and β_2 integrins mediate activated B cell binding to antigen-presenting follicular dendritic cells in germinal centers (*41*). Importantly, the adhesive function of lymphocyte integrins (and other adhesion receptors such as CD44) can be regulated over the time frame of lymphocyte crawling in tissues by signaling through many cell surface receptors including not only chemoattractant receptors but also adhesion receptors themselves and an array of Ig family members including the T and B cell antigen receptors and their associated costimulatory molecules (*21, 42*). Indeed, cells must continuously integrate pro-adhesive and potentially anti-adhesive signals from diverse cell surface receptors that may be engaged coordinately in complex in vivo environments. The GTP-binding protein RhoA may play an essential role in this process, acting as an intracellular control point in signaling from chemoattractant and other receptors to lymphocyte integrins (*35*).

Several classes of soluble factors and their receptors have been implicated in the regulation of lymphocyte locomotion, including a variety of cytokines and growth factors [IL-2, IL-10, TGF-β1, hepatocyte growth factor, and vasoactive intestinal peptide (*43*)]. However, because of their diversity, widespread tissue expression, and chemotactic specificity for functionally distinct lymphocyte subsets, the chemokines (and other chemoattractants that may act through homologous serpentine receptors) have received particular attention. More than 30 chemokines and five chemokine receptors have been identified (*7, 44*). Many chemokines and their lymphocyte receptors are induced or modulated during inflammation, rendering them strong candidates for regulating altered lymphocyte targeting during immune and inflammatory responses. Chemokines can also bind and be presented differentially by various glycosaminoglycans, suggesting that haptotactic responses to substrate or cell-bound chemokines may be as or more important than classic chemotaxis in directing migration (*45*).

Finally, whereas antigen receptors play no direct role in the selectivity of lymphocyte extravasation from blood (*3, 46*), antigen is critically important in regulating microenvironmental homing properties of lymphocytes. For example, antigen-specific T cells are initially cleared from the recirculating lymphocyte pool after antigen administration (*46*), and migrating antigen-specific plasmablasts and memory T cells become locally enriched through retention (and probably also preferential proliferation) at sites of antigen deposition [reviewed in (*3*)]. The retention of antigen-reactive cells is due, at least in part, to activation of integrin adhesion through the engagement of antigen-receptor and costimulatory pathways, and indeed, such integrin activation has been directly demonstrated for T cells undergoing the naïve to memory/effector transitions in secondary lymphoid tissues in vivo (*13*). Specific antigen can also redirect microenvironmental homing within tissues. For example, antigen-specific $CD4^+$ T cells have been noted to translocate from paracortical T zones to B cell follicles upon antigen stimulation (*47*).

Homing and Immune Homeostasis

It is axiomatic that the homeostasis of mature lymphocyte populations must involve competition: Although displaying some variability with recent immune activity and some decline in progenitor production with age, the major populations of circulating B and T cells, especially memory cells, are maintained within a limited normal range of cell numbers and frequency during adult life (*48–50*). Thus, naïve B and T cells emigrating from the bone marrow and thymus must compete with existing naïve cells for entry into the recirculating lymphocyte pool. Similarly, as the memory cells responsible for immunity are limited in overall number, it follows that cells mediating immunity to a prior antigen must compete for existence with memory cells arising in response to new antigens. How would such competition occur? Recent studies support the concept that competitive homing to microenvironmental niches is a critical control mechanism of lymphocyte homeostasis.

In this model, competition for access to specialized microenvironments, and thus for the trophic or regulatory factors they provide, determines the balance between cell survival, expansion, differentiation, and death (Fig. 4). The microenvironmental factors required for survival are likely unique for each type of lymphocyte and are provided in limited quantity in particular microenvironmental "niches" that will also vary for each lymphocyte type (such as B versus T cells, memory versus naïve cells, and $CD4^+$ versus

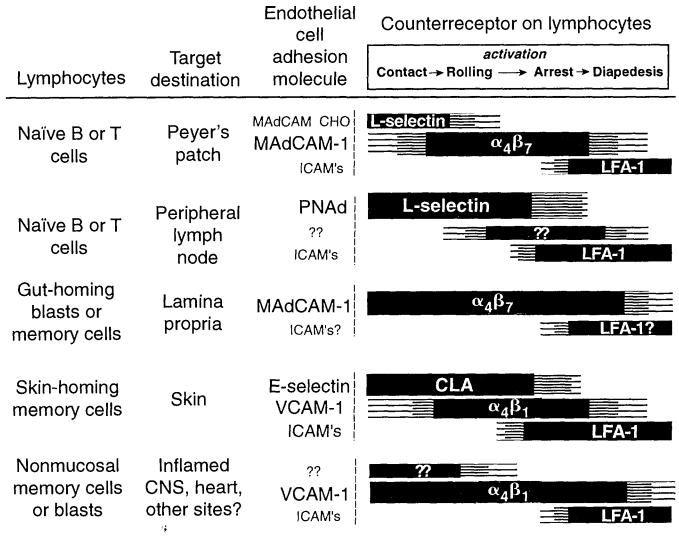

Fig. 3. Known or hypothesized adhesion-decision cascades conferring specificity of lymphocyte homing in different sites. As indicated, the homing receptor phenotype of naïve lymphocytes allows them access to lymph nodes and Peyer's patches, but not to inflammatory extralymphoid tissues. In contrast, distinctive subsets of memory/effector cells express phenotypes that allow their targeted access to skin, lamina propria, and potentially other sites such as joints. Quantitative as well as qualitative regulation of receptors is critical to specificity control. The overlap of bars emphasizes overlapping functions in particular settings, and the vertical width of bars (and font sizes) indicate the relative expression level and functional importance of each component in the cascade, which may of course be variable. Activating signals are unknown, and may not be required for arrest of immunoblasts expressing preactivated integrins. Questionable (or potentially variable) involvement of unidentified pathways is indicated by question marks. It should be mentioned that tissue-selective cascades can be altered both developmentally and as a function of severe local inflammation, which can lead to more promiscuous lymphocyte recruitment (*10*).

$CD8^+$ cells). These protective niches are both finite in number and limited in overall capacity to provide viability support. When supportive niches are overcrowded, competition for access is increased, and cell death will occur until a balance between cell number and supportive factors is again achieved. Conversely, when a niche is empty, the available survival factors would support the viability of most or all cells re-seeding the locale until the niche is repopulated and competition is resumed. In addition to trophic cytokines, molecules involved in microenvironmental homing are themselves prime candidates as survival regulatory factors; for example, engagement of integrins (for instance, during germinal center cell interactions with VCAM-1 on follicular dendritic cells) can deliver potent apoptosis-inhibiting signals (*21, 41*). The molecular control of this balance between lymphocyte expansion and death is a topic of intense investigation. As examples, the role of Fas, Fas-ligand, CTLA-4, and IL-2 receptor α in braking lymphoid expansion and of BCL-2 in protecting against cell death has been graphically illustrated in knock-out or mutant mice functionally lacking these molecules, which show syndromes of progressive lymphoid tissue hyperplasia or atrophy, respectively (*51*).

Systemic as well as microenvironmental homing mechanisms play a critical role in this process. First, the continuous exchange of lymphocytes between their particular microenvironments and the recirculating lymphocyte pool provides the "stirring" mechanism by which the overall repertoire of a given lymphocyte subset is repeatedly exposed to the culling effect of niche competition. Such mixing facilitates a survival of the fittest, or more aptly, a survival of the most appropriate clones out of the overall repertoire. Systemic recirculation through secondary lymphoid organs may be critical for the deletion or tolerance of naïve B and T cells reactive against regional or tissue-specific self-antigens. Moreover, just as segregation into distinct microenvironmental domains prevents inappropriate competition between unrelated lymphocyte subsets (for example, T versus B cells), the tissue selectivity of lymphocyte recirculation prevents inappropriate competition between memory cells specific for tissue-restricted antigens, targeting them to regions of the body (for example, mucosa or skin) most likely to retain or reexperience their respective antigens and thus to provide optimal microenvironmental support.

An important implication of this model is that homeostasis is not determined solely by the characteristics of individual cells, but also by the total number and diversity of competing cells. In extreme situations, the lack of competition may not only facilitate extended survival of lymphocytes but may even unveil a (normally suppressed) potential for expansion. For example, naïve T cells are thought to be a relatively stable, nonproliferating population in adult mice and humans (*48–50*). However, in alymphocytic or T cell–deficient mice with no competition for supportive niches, adoptively transferred mature naïve and memory T cells display a surprising capacity for repopulation of the recirculating pool [reviewed in (*48, 50*)]. Such expansion is likely driven by nonantigenic as well as antigenic stimuli. Consistent with the complex role of the microenvironment in this process, the extent of expansion and repopulation is characteristically different in different hosts (normal, severe combined immunodeficiency disease (SCID), nu/nu, or "B" mice) (*50*). Moreover, lymphocyte subsets interact in influencing each other's homeostasis in such models (*50*), emphasizing that lymphocytes can themselves contribute to homeostatic environments. For example, CD8 cells can reduce the expansion of CD4 cells in nude recipients [reviewed in (*50*)], and B cells dramatically enhance the longevity of CD4 memory T cells (*52*).

Altered competitive situations may be important clinically as well. After conventional bone marrow transplantation where the thymus is hypofunctional because of age or other factors, donor mature T cells present in the bone marrow inoculum can repopulate the recipient recirculating pool (*53*). During the expansion of lymphoid cells in essentially empty lymphoid microenvironments, the competition for supportive niches would be relaxed, potentially allowing survival and differentiation of self-reactive lymphocytes that would normally be deleted or rendered anergic. Such a mechanism may be a contributing factor in the development of the autoimmune-like syndrome of chronic "graft versus host" disease after bone marrow transplantation (*54*). Inefficient competitive culling may also help explain the paradoxical development of autoimmunity in patients with relative deficiencies of circulating B or T cells (*55*).

A variety of other well-described immunologic phenomena can also be interpreted in light of these concepts. The importance of antigen to the survival and function of adoptively transferred memory cells may be due to the competitive advantage antigen provides in competition with irrelevant memory cells for microenvironmental support. Indeed, the controversy over whether antigen persistence is required for the maintenance of immunologic memory (*8, 48*) may reflect a variable competitive environment for the memory cells in different experimental models; in some systems, persistent antigen may be required to give the studied memory population a competitive advantage, whereas in other systems such competition may be less stringent, obviating the need for such help. That antigen can provide a competitive advantage for lymphocyte survival is clearly demonstrated by the selection of cells with high-affinity antigen receptors during the development of B and T cell memory (*48*). Antigen, however, does not always provide a prosurvival advantage. In circumstances of profound antigenic stimulation, such as may occur with superantigens or some viral infections, there can be a complete depletion of responding T cells [reviewed in (*8, 48*)]. Although "overstimulation" has been postulated as a mechanism of T cell deletion in these settings, this phenomenon might also reflect niche overcrowding; the simultaneous activation of large numbers of cells by

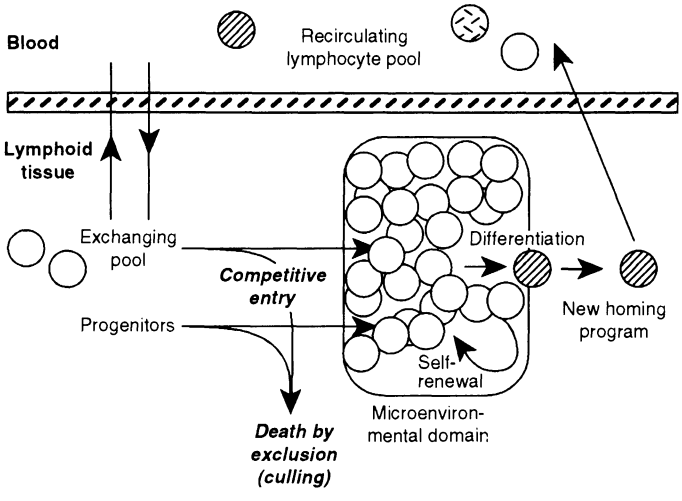

Fig. 4. Schematic summary of the proposed role of recirculation and microenvironmental homing in lymphocyte homeostasis. In this model, competitive homing to specialized microenvironments determines access to supportive trophic and regulatory factors, and thus the balance between cell survival, differentiation, and death. Lymphocyte recirculation (although not itself competitive at the level of extravasation) ensures that competition for shared microenvironmental niches, and thus competitive culling, can act on the entire immune repertoire of a given lymphocyte subset. Although not considered here, the model would also encompass competition for nonsupportive microenvironments involved in active killing of targeted lymphocytes (in which case excluded lymphocytes would have a survival advantage).

strong stimuli, with each cell jostling for the same niche, may overwhelm the ability of even the appropriate microenvironments to provide viability support. Taken together, these considerations would predict that in the "Darwinian" struggle for microenvironmental support, the longevity of antigen-specific memory responses would be variable, depending on the intensity and diversity of subsequent immune stimuli. Such factors as the relative affinity of antigen receptors for foreign versus self-antigen, cytokine synthesis and response patterns, and recirculation behavior likely combine to determine the overall competitiveness of a given cell for long-term survival.

The interplay between competitive niche homing, microenvironmental support, and antigen is well illustrated by recent studies of naïve B cells in transgenic models (*55*, *56*). Previous investigators had established that the bone marrow exports more naïve B cells than can be absorbed in the periphery, and that there must be a mechanism for restricting the entry of newly produced B cells into the long-lived, recirculating B cell pool (*57*). When homogeneous hen egg lysozyme (HEL)–specific B cells are transferred into normal recipients, they home to follicles and join the recirculating B cell pool. In recipients expressing transgenic HEL as a "pseudo-autoantigen," however, HEL-specific B cells are competitively excluded from follicles, accumulating in the surrounding outer T zone where they undergo apoptosis. Exclusion is thought to represent competition with the resident polyclonal B cell population for follicular homing, because when all B cells are HEL-specific (in double HEL Ig–HEL transgenics), they successfully enter follicles and the recirculating lymphocyte pool as phenotypically naïve cells, in spite of continuing antigen exposure. Competitive antigen-dependent localization to a scattered selective microenvironment in the outer T zone may also play a role in these models. Although the mechanism of competition is unknown, Cyster *et al.* (*55*) concluded that the presence of autoantigen puts B cells at a competitive disadvantage with respect to homing into the supportive niche of B cell follicles and ultimately results in their elimination. These studies illustrate the fundamental participation of homing mechanisms in niche competition and support a critical role for these processes in eliminating autoreactivity and shaping the B cell repertoire. Parallel studies in T cell receptor transgenic systems may enable definition of competitive homing environments for the homeostasis of T cell subsets.

Conclusion

In this discourse, we have emphasized recent conceptual advances in lymphocyte homing and homeostasis, including (i) combinatorial construction of specific homing pathways, (ii) bidirectional "cross-talk" between lymphocyte and microenvironment leading to continuous adjustment of migratory behavior, and (iii) the roles of competitive niche homing in controlling lymphocyte homeostasis and shaping the immune repertoire. Further work is required to test these models critically, to unravel the molecular and cellular basis for these complex physiologic processes, and to apply this understanding to immunologic disease.

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