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Road signs guiding leukocytes along the inflammation superhighway

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The term *inflammation* is used to describe the localized tissue changes, including leukocyte extravasation, that occur as part of the response to tissue damage, infection, or other immunologic responses. This carefully orchestrated series of events requires the existence of highly specific, regulated mechanisms for control of leukocyte recruitment and is dependent on both the inciting event and organ involved. This review summarizes recent developments in our understanding of how adhesion molecules and chemokines interact to facilitate tissue-specific and leukocyte subtype–specific influx during inflammation. Novel mechanisms believed to be responsible for capture and compartmentalization of B and T lymphocytes within lymph nodes are discussed, along with a description of adhesion molecule– and chemokine-mediated pathways that are believed to be involved in selective recruitment of lymphocytes and eosinophils to a variety of tissues, including the skin, gut, and lung. This growing knowledge and its potential importance provide enthusiasm for future anti-inflammatory therapies that target these recruitment pathways. (J Allergy Clin Immunol 2000;106:817-28.)

Key words: *Eosinophils, lymphocytes, homing, recruitment, adhesion molecules, chemokines, skin, gastrointestinal tract, lung, lymph nodes*

Abbreviations used

BALT:	Bronchus-associated lymphoid tissue
BLC:	B-lymphocyte chemoattractant
CLA:	Cutaneous lymphocyte antigen
CTACK:	Cutaneous T-cell–attracting chemokine
GALT:	Gut-associated lymphoid tissue
HEV:	High endothelial venule
ICAM-1:	Intercellular adhesion molecule-1
IP-10:	IFN-inducible protein-10
I-TAC:	IFN-induced T-cell α-chemoattractant
Le^x:	Lewis X
LFA-1:	Lymphocyte functional antigen-1 (CD11b/CD18)
Mac-1:	Macrophage associated antigen-1 (CD11b/CD18)
MAdCAM-1:	Mucosal addressin cell adhesion molecule-1
MCP:	Monocyte chemoattractant protein
MDC:	Macrophage-derived chemokine
Mig:	Monokine induced by IFN-γ
MIP:	Macrophage inflammatory protein
plt:	Paucity of lymph node T cells
PNAd:	Peripheral lymph node addressin
PSGL-1:	P-selectin glycoprotein ligand-1
SDF:	Stromal cell–derived factor
SLC:	Secondary lymphoid tissue chemokine
TARC:	Thymus- and activation-related chemokine
TECK:	Thymus-expressed chemokine
VCAM-1:	Vascular cell adhesion molecule-1
VLA:	Very late activation antigen (β1 integrins)

The phrase "rubor et tumor cum calore et dolore" or "redness and swelling with heat and pain" is attributed to the first century AD writings of the roman author Cornelius Celsus.[1] His initial clinical description of inflammation was modified in the 1800s by Rudolf Ludwig Karl Virchow to include "functio laesa" or "disturbed function" to include the observation that inflamed tissues do not function normally. However, it was Julius Conheim, a student of Virchow, who is credited with making the observation that inflammation also includes plasma exudation and local leukocyte extravasation into the affected tissue. These concepts still hold true for the current definition of inflammation, which includes the phenomena of local vascular changes in diameter and blood flow, increased vascular permeability, and leukocyte infiltration. Conditions associated with inflammation range from infection to repair of injured tissue, and it is clear that the development of leukocytic infiltrates involves mechanisms that can be unique or overlapping depending on the cell type and tissue location.

The purpose of this review is to summarize recent advancements in our understanding of how adhesion molecules and chemokines combine to facilitate tissue-specific and leukocyte subtype–specific accumulation of leukocytes during inflammation. Exciting new information regarding the architecture of lymph nodes and the mechanisms by which naive B and T lymphocytes accumulate within lymph nodes is included. Also, for illustrative pur-

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poses and because of their relevance to allergic inflammation, this review will emphasize mechanisms involved in trafficking of T cells and eosinophils to a variety of tissues including skin, gut, and lung. Given the expansive nature of the topic, however, the reader is referred to other recent reviews for additional information.[2-9]

GENERAL AND PREFERENTIAL MECHANISMS OF LEUKOCYTE EXTRAVASATION

Regardless of the cell type involved, the process of leukocyte recruitment into tissues is believed to involve a series of steps, the earliest of which begin when circulating cells undergo margination, resisting the shear forces associated with blood flow.[10] Adhesion molecules are necessary for these interactions to occur, and it is now believed that selectins (L-selectin, P-selectin, and E-selectin) and their carbohydrate-containing counterligands mediate the initial margination steps involving tethering and rolling. Although all leukocytes express selectins or selectin ligands, one potential mechanism for preferential leukocyte recruitment during inflammation involves the levels of surface expression of these selectins and selectin ligands, which differ among leukocytes (Table I). For example, L-selectin is an important ligand for leukocyte migration into many locations, including lymph nodes and other secondary lymphoid tissues. Levels of L-selectin are higher on lymph node–homing T cells, and this may facilitate their accumulation within this site by enhancing binding to locally expressed ligands such as PNAd.[11,12]

Other selectin-mediated adhesion processes appear to be regulated by rapid reduction in expression. For example, exposure of granulocytes to most chemoattractants causes irreversible shedding of L-selectin within minutes, preventing further use of this adhesion pathway, perhaps allowing other pathways to take over.[13,14] Leukocyte activation also leads to rapid release of PSGL-1 from the cell surface and marked reductions in P-selectin adhesion. Unlike the mechanism involved in L-selectin shedding, the mechanism for PSGL-1 shedding does not involve any of the know matrix metalloproteases.[15] Thus the state of activation may influence the contribution of both L-selectin and PSGL-1 in mediating cell adhesion.

Levels of selectin ligands expressed on various leukocytes may also contribute to preferential cell recruitment responses. For example, human eosinophils express about twice as much of PSGL-1 than do neutrophils, and the interaction of eosinophils with P-selectin is generally of greater magnitude than that for neutrophils.[16-18] In addition, lower levels of P-selectin expression on endothelium may favor eosinophil attachment over neutrophil attachment.[19] P-selectin is also interesting because both histamine and sulfdopeptide leukotrienes, mediators released at sites of allergic inflammation, are effective at inducing P-selectin expression.[20,21] Another example of how differences in levels of selectin ligands may control initial steps in leukocyte emigration relates to expression of sialyl-dimeric Le^x, a ligand on granulocytes for E-selectin. Here, neutrophil interaction with E-selectin is favored because they express approximately 10 times as much of this E-selectin ligand than do eosinophils.[22]

Subsequent to selectin and selectin ligand interactions, the process of firm leukocyte adhesion and transendothelial migration involves different subsets of adhesion molecules, termed integrins, and Ig gene superfamily members.[10] Examples of the former include the β1, β2, and β7 integrins, whereas examples of the latter include VCAM-1, intercellular adhesion molecule-1 (ICAM-1), and MAdCAM-1. For example, the α4 integrins (α4β1 [also known as VLA-4 or very late activation antigen-4] and α4β7) display somewhat restricted surface expression in that both these ligands are absent from the surface of human neutrophils. Therefore, expression of their cytokine-inducible endothelial counterligands (VCAM-1 and MAdCAM-1) at sites of inflammation favors recruitment of all leukocytes except for neutrophils (Table I).

Among the β2 integrins, all leukocytes express the β2 integrin lymphocyte functional antigen-1 (LFA-1) or CD11a/CD18 and can bind to its major counterligand, ICAM-1, found constitutively on endothelium, epithelium, and other cell types. Another ICAM-1 ligand, macrophage associated antigen-1 (Mac-1) or CD11b/CD18, is not expressed by most lymphocytes but is prominently expressed by all other leukocytes.[10] LFA-1 and Mac-1 are particularly important during the process of firm adhesion and transendothelial migration of leukocytes, regardless of cell type. Instead of the relative levels of cell surface expression, it is felt that the activation state of this integrin is more important.[23] This is one place where chemokines, through their specific seven transmembrane, G-protein–coupled receptors, are felt to play an important role in shaping the cellular mix of the inflammatory infiltrate.[2,24] It has been proposed that exposure to chemokines at or near the endothelial luminal surface rapidly stimulates affinity of the LFA-1/ICAM-1 interaction and that this activation is critical for leukocyte capture on the endothelial cell.[8,25,26] This mechanism may be similar for the α4 integrins because activation of T cells through seven transmembrane receptors has been reported to enhance adhesion to VCAM-1 or MAdCAM-1.[27,28] However, studies with eosinophils are conflicting in that chemokine exposure has been reported to enhance or reduce adhesion to VCAM-1, or both, depending on the methods and duration of exposure.[29-31] Because cells must detach during directional migration,[32] other events, such as regulation of function and redistribution of integrins on the cell surface, also occur as a result of exposure to chemokines.[33]

Differences in chemokine receptor expression on leukocytes are certain to play a major role in selective cell recruitment. This topic has been recently reviewed elsewhere.[2,24,34,35] For purposes of this review, Table I includes examples relevant to cell trafficking to lymph nodes, skin, gut, and lung that are discussed in the next section. Some of these pathways appear to be tissue specific, whereas others are leukocyte specific. As examples of the latter situation, expression of CCR3 on eosinophils

TABLE I. Examples of how differential surface expression of adhesion molecules and chemokine receptors on human leukocytes can contribute to selective cell recruitment

Leukocyte surface structure	Ligands	Pattern of leukocyte expression
Adhesion molecules		
L-selectin	PNAd, others	All leukocytes, but naive T cells > memory T cells
PSGL-1	P-selectin	All leukocytes, but eosinophils > neutrophils
CLA	E-selectin	Skin-homing memory T cells
Sialyl-dimeric Le^x	E-selectin	All leukocytes, but neutrophils > eosinophils
α4β1 integrin	VCAM-1, others	All leukocytes except neutrophils
α4β7 integrin	MAdCAM-1, others	All leukocytes except neutrophils
αEβ7 integrin	E-cadherin	Intraepithelial lymphocytes
Chemokine receptors		
CCR3	Eotaxin 1-3, others	Eosinophils, basophils, mast cells; some T_H2 cells
CCR4	TARC, MDC	Skin-homing memory T cells
CCR5	MIP-1β	T_H1 cells
CCR6	MIP-3α	Memory T cells
CCR7	SLC, MIP-3β	Naive B and T cells
CCR8	I-309	T_H2 cells
CCR9	TECK	Gut-homing memory T cells
CCR10	CTACK	Skin-homing memory T cells
CXCR3	Mig, IP-10, I-TAC	T_H1 cells
CXCR5	BLC	Naive B cells

PNAd, Peripheral lymph node addressin; *PSGL-1,* P-selectin glycoprotein ligand-1; *CLA,* cutaneous lymphocyte antigen; *Le^x,* Lewis X; *VCAM-1,* vascular cell adhesion molecule-1; *MAdCAM-1,* mucosal addressin adhesion molecule-1; *TARC,* thymus- and activation-related chemokine; *MDC,* macrophage-derived chemokine; *MIP,* macrophage inflammatory protein; *SLC,* secondary lymphoid tissue chemokine; *TECK,* thymus-expressed chemokine.

allows them to respond to eotaxin and related chemokines.[2] Cytokine priming, as occurs for instance when eosinophils are exposed to IL-5, markedly potentiates responses to chemokines[36,37] and shifts integrin usage away from β1 integrin-mediated pathways while up-regulating β2 integrin-mediated events.[31,38] Naive T cells express CCR7 and CXCR5, whereas memory T cells preferentially expresses CCR4 and CCR6.[5] Expression of CCR4 amd CCR8, as well as perhaps CCR3, has been associated with the T_H2 phenotype,[39-41] but this still remains controversial, especially with respect to CCR3.[42,43] In contrast, expression of CCR5 and CXCR3 has been associated with T_H1 cells.[40,41,44] Thus the type of chemokines encountered and whether the leukocyte is activated, differentiated, or primed can influence which subsets of leukocytes get recruited.

TISSUE-SPECIFIC MECHANISMS FOR LEUKOCYTE EXTRAVASATION

Lymph node homing

Until recent years, the mechanisms responsible for the architectural arrangement of lymph nodes have remained a mystery. Several developments, however, regarding adhesion molecules and chemokines have begun to shed light on this important issue (Fig 1).[5,8] Progress in this area was initiated by studies demonstrating that antibodies to adhesion molecules, such as L-selectin, reduce lymphocyte attachment to PNAd on HEVs in lymph nodes.[45] Subsequent studies in L-selectin–deficient mice revealed markedly reduced development of lymph nodes, with few accumulated B and T lymphocytes.[46] Besides L-selectin/PNAd interactions, a role for ICAM-1/LFA-1 in lymphocyte homing to secondary lymphoid organs has been demonstrated.[47] It also appears that the cytokine lymphotoxin and its TNF family receptor are critical for the development of lymph nodes and Peyer's patches.[4]

In addition to adhesion molecules and cytokines, a key role for chemokines in directing the localization of lymphocytes within lymph nodes has been discovered. One breakthrough came from the study of a mutant strain of mice (the *plt* strain, for "paucity of lymph node T cells") possessing lymph nodes and Peyer's patches deficient in T cells.[48] This strain of mice is deficient in the gene for the chemokine SLC, which is a ligand for the chemokine receptor CCR7.[49,50] Normal T cells infused into *plt*-deficient mice fail to accumulate in lymph nodes.[51,52] Remarkably, injection of the missing SLC chemokine into these mice leads to its uptake and display along the HEV of the draining lymph nodes, restoring T-cell homing to those lymph nodes.[52] Studies of normal mouse lymph nodes using in situ hybridization demonstrated prominent expression of SLC (also called TCA-4, 6Ckine, and Exodus-2) in the T-cell zones and its virtual absence from B-cell zones.[5] In vitro SLC is effective in triggering integrin-dependent arrest of CCR7-bearing T cells.[27,49] In addition, it appears that T_H1 and T_H2 cells tend to home to different regions within lymph nodes. CCR7 is more consistently expressed by T_H1 cells than by T_H2 cells, and genetically forced expression of CCR7 on T_H2 cells changes their lymph node homing pattern to that of T_H1 cells.[53] The story is still incomplete, however, because CCR7 knockout mice have markedly reduced numbers of both T and B lymphocytes in lymph nodes.

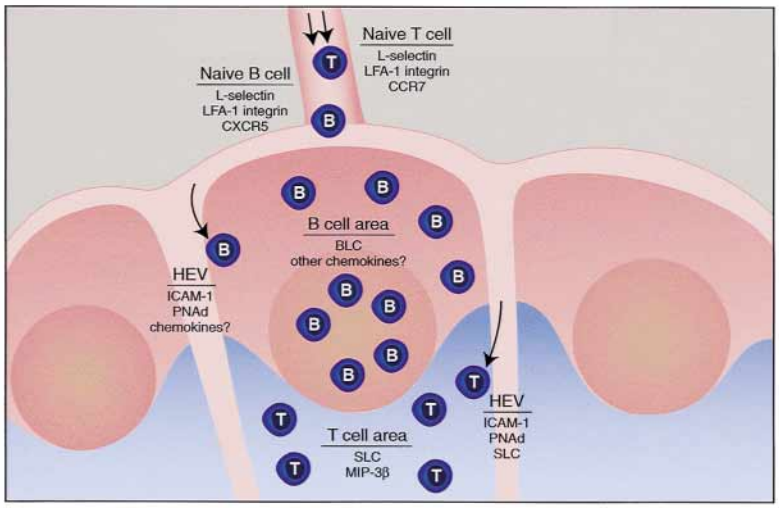

FIG 1. Potential role of adhesion molecules, chemokines, and chemokine receptors in lymphocyte homing to lymph nodes. For naive T cells, interactions with the high endothelial venule *(HEV)* occur by L-selectin/PNAd and ICAM-1/LFA-1 integrin and are stimulated by HEV-displayed SLC (by CCR7). Subsequently, their positional localization within the lymph node may then be controlled by production of MIP-3β (also by CCR7) within the T-cell zone. Similar pathways appear to exist for naive B lymphocytes, except that BLC (by CXCR5) controls localization within the B-cell zone, and other, as yet unidentified HEV-displayed chemokines appear to be involved.

Indeed, numbers of B cells, and B-cell homing, are less affected in *plt* mice, suggesting that SLC is not critical for B-cell accumulation in lymph nodes.[54,55] It has thus been hypothesized that another chemokine is important for B-cell homing to lymph nodes, but to date its identity remains unknown. It is also possible that B-cell homing is T-cell dependent.

Another CCR7-active chemokine localized to the T-cell zone and implicated in lymphocyte trafficking within lymph nodes is the chemokine MIP-3β (also called ELC or Exodus-3). Unlike SLC, which is displayed along the lumen of the HEV as well as within the T-cell area, MIP-3β is not found on HEV but is present in the T-cell area. It has therefore been hypothesized to play a role in the positional localization of T cells within the lymph node rather than their capture per se.[5] There is also a small subset of circulating $CD4^+$ T cells, called effector memory cells, that lack CCR7[56]; these cells may be unable to enter lymph nodes, and instead home to inflammatory sites in nonlymphoid organs where they could play a role in antigen-specific responses.

One additional chemokine receptor, CXCR5 (a ligand for the chemokine BLC, also called BCA-1), is found predominantly on B cells. Unlike SLC or MIP-3β, BLC has been localized by in situ hybridization to the B-cell follicles of lymph nodes, spleen, and Peyer's patches, and mice deficient in CXCR5 have diminished development of B-cell follicles.[57] Ectopic production of BLC in pancreatic islet cells of genetically manipulated mice results in local B-cell accumulation.[58] As mentioned above, both CCR7 and CXCR5 are found on naive lymphocytes, consistent with the habit of these cells to traffic and lodge within secondary lymphoid organs.[8] Presumably, the inability of granulocytes such as eosinophils to home to lymph nodes is due to their lack of expression of CCR7 and CXCR5 because they express the same pattern of adhesion molecules (eg, L-selectin and LFA-1, see below).

Skin homing

Memory lymphocytes can enter virtually any inflamed tissue in the body to perform antigen-specific surveillance.[6] These memory cells, which express CD45RO instead of CD45RA, are selectively recruited after allergen challenge of the skin.[59] Although the majority normally reside in mucosal sites, eosinophils can also accumulate in the skin.[60,61] It is now clear that specific adhesion molecules and chemokines regulate T-cell and eosinophil trafficking to inflamed skin (Fig 2).

With respect to lymphocytes, one of the first adhesion molecules implicated in T-cell homing to the skin was CLA.[62,63] CLA serves as a ligand for E-selectin (formerly called ELAM-1 or endothelial-leukocyte adhesion molecule-1) and is only found on activated memory skin homing T cells,[64,65] and in contrast CLA^+ T cells are not found in the gut or the lung.[64,66] Its ligand, E-selectin, is induced de novo on inflamed postcapillary endothelium, especially in skin.[63,67] Studies in both animals and humans have confirmed the important role for CLA during most, if not all, cutaneous inflammatory responses.[60,64] However, it must be noted that in leukocyte adhesion deficiency type II (the congenital defect in fucose metabolism resulting in defective selectin ligand synthesis), an increased susceptibility for skin infections is not observed, and T-cell recruitment to skin is normal.[68,69] Other murine studies have implicated the integrins $\alpha 1\beta 1$ and $\alpha 2\beta 1$ in T-cell accumulation during contact and delayed-type hypersensitivity reactions in the skin, pre-

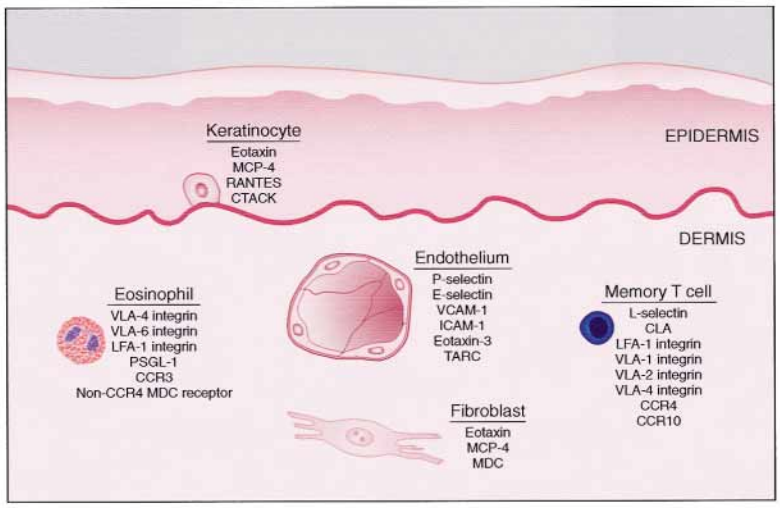

FIG 2. Potential role of adhesion molecules, chemokines, and chemokine receptors in the accumulation of eosinophils and lymphocytes during T_H2-type inflammatory responses in the skin. Recruitment of memory CLA+ T cells to the skin during allergic cutaneous inflammation involves initial interactions by E-selectin/CLA, ICAM-1/LFA-1, and VCAM-1/VLA-4, perhaps stimulated by endothelial-displayed TARC (by CCR4). Subsequent localization within tissues may then be controlled by local production of other chemokines such as MDC (also by CCR4) and CTACK (by CCR10), and interactions between β1 integrins and tissue matrix proteins such as fibronectin and collagen. Eosinophil migration into the skin during allergic cutaneous inflammation probably involves initial interactions by P-selectin/PSGL-1, ICAM-1/LFA-1, and VCAM-1/VLA-4, perhaps driven by endothelial display of eotaxin and eotaxin-3 (by CCR3). Subsequent localization of eosinophils within tissues may then be controlled by dermal and epidermal production of identical or related CCR3-active chemokines as well as MDC, and interactions between β1 integrins and tissue matrix proteins such as fibronectin (by VLA-4) and laminin (by VLA-6).

sumably because the interactions between these receptors and their matrix protein ligands (eg, collagen) are necessary for dermal localization.[70]

Also important for leukocyte accumulation in the skin are the β2 integrins. Nowhere is this more evident than in leukocyte adhesion deficiency type I (the congenital deficiency of β2 integrins), where skin infections are especially frequent; these sites are devoid of neutrophils (which require β2 integrins for ICAM-1–mediated recruitment) and have reduced, but not absent, numbers of other leukocytes (which also require β2 integrins for ICAM-1–mediated recruitment but also express VLA-4 and thus can also use VCAM-1 for accumulation).[69]

Although adhesion molecules are necessary for skin homing, another layer of complexity and selectivity at the level of chemokines and their receptors has now emerged. The chemokine receptor CCR4 is highly expressed on the surface of CLA+ memory T cells, especially the T_H2 subset.[39,40] Ligands for CCR4, such as the chemokine TARC, appear in lesional skin in a mouse model of atopic dermatitis.[71] TARC has been detected in venules of inflamed human skin (but not in intestinal mucosa); it is produced by endothelial cells and stimulates T-cell adhesion to ICAM-1 in vitro.[39] Another CCR4-active chemokine, MDC, has also been implicated in this dermal response, but the kinetics and levels of production are less compelling.[71] A separate study suggests that MDC can stimulate eosinophil chemotaxis through a non-CCR4–dependent mechanism and therefore may contribute to eosinophil accumulation.[72] Yet another chemokine, CTACK (also called ESkine), preferentially activates homing to the skin of memory CLA+ T cells. This chemokine, produced by keratinocytes within the skin, activates cells through another chemokine receptor, CCR10.[73,74]

Adhesion molecules and chemokines are also important for accumulation of eosinophils in the skin (Table I and Fig 2).[60] Human eosinophils express high levels of PSGL-1 and L-selectin, as well as all four of the β2 integrins.[75] Among the β1 integrins, human eosinophils express VLA-4 and VLA-6, the latter being a ligand for laminin.[76] With regard to chemokine receptors, eosinophils do not express CCR4,[72] but they do express CCR1, CCR3, and CXCR4.[77,78] Among their possible ligands, it appears that CCR3-active chemokines (eg, RANTES, eotaxin, eotaxin-2, and monocyte chemoattractant protein [MCP]-4) are primarily implicated in eosinophil accumulation in the skin after allergen challenge in humans.[79-82] In skin biopsy specimens from patients with atopic dermatitis, increased levels of the endothelial adhesion molecules VCAM-1 and P-selectin[83] and the chemokines eotaxin and MCP-4[84,85] are seen. Intradermal injection of RANTES caused rapid and selective accumulation of eosinophils in allergic subjects.[86] Similar to findings in vitro, eosinophil accumulation after eotaxin injections in mice is markedly potentiated by IL-5.[87] Consistent with in vitro findings, intradermal injection of eotaxin-3, a chemokine that is produced by IL-4– or IL-13–activated endothelial cells, caused selective eosinophil recruitment in cynomolgus

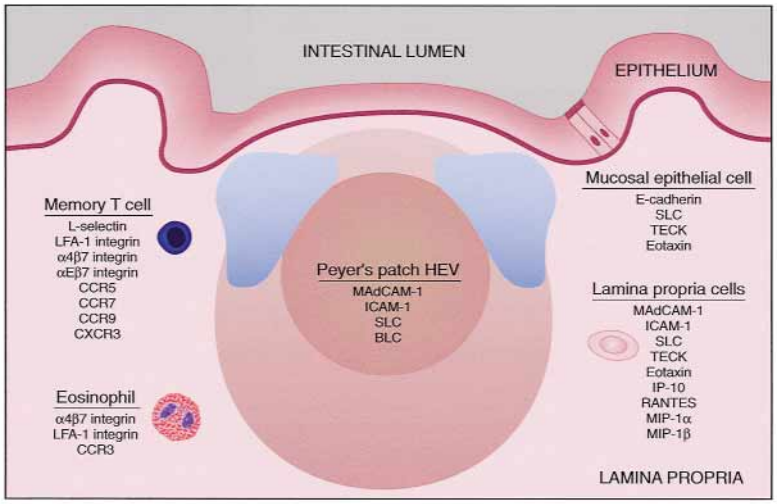

FIG 3. Potential role of adhesion molecules, chemokines, and chemokine receptors in the accumulation of eosinophils and lymphocytes in the gut. This figure combines mechanisms involved in normal homing responses and in inflammatory responses. Homing of lymphocytes to sites in Peyer's patches and lamina propria in the gut involves initial interactions via ICAM-1/LFA-1 integrin and MAdCAM-1/L-selectin/α4β7 integrin, perhaps stimulated by TECK (by CCR9) or SLC (by CCR7). For B cells, local production in Peyer's patches of other chemokines such as BLC (acting through CXCR5) may also be important (not shown). Chemokines such as IP-10 (by CXCR3), RANTES, MIP-1α, and MIP-1β (each through CCR5) may also influence lymphocyte accumulation within the lamina propria under both inflamed and noninflamed conditions. A further subset of the gut-homing T cells that express CCR5 and CXCR3 also express αEβ7 integrin and can migrate into the epithelium (the so-called intraepithelial lymphocyte), where they interact with E-cadherin, an αEβ7 integrin ligand. For eosinophils, interactions implicated in their accumulation in gastrointestinal tissues include ICAM-1/LFA-1 integrin, VCAM-1/VLA-4 integrin, and MAdCAM-1/L-selectin/α4β7 integrin, perhaps influenced by eotaxin (through CCR3).

monkeys.[88,89] Eotaxin-3 is particularly intriguing because IL-4 and IL-13 also have the ability to selectively induce endothelial expression of VCAM-1[90,91] and P-selectin[92,93] and endothelial and dermal fibroblast production of eotaxin,[94] which together have been shown to be important in eosinophil accumulation in animal models of eosinophilic dermal inflammation.[60,82]

Gut homing

A good example of specificity of leukocyte accumulation within tissues is that seen in the gastrointestinal tract.[6] The so-called GALT (gut-associated lymphoid tissue) includes specialized structures such as Peyer's patches, considered to be secondary lymphoid organs where nests of T and B lymphocytes accumulate in a pattern that bears some resemblance to that observed in lymph nodes. In addition to harboring lymphocytes, the gastrointestinal tract represents the largest reservoir of eosinophils within the body. It therefore comes as no surprise that several adhesion and chemokine-dependent pathways, some unique, are used for homing of leukocytes to the gut (Fig 3).

With respect to adhesion molecules, L-selectin, LFA-1, and ICAM-1 were among the first suspected to be involved in gut homing.[47,95,96] Inflamed intestine expresses increased levels of VCAM-1, ICAM-1, and E-selectin, and early trials with antagonists of ICAM-1 for Crohn's disease sound promising.[97] Indeed, patients with leukocyte adhesion deficiency type I and type II have stomatitis, gingivitis, and periodontitis, but only those with type I disease have perianal abscesses, peritonitis, and necrotizing enteritis.[69,98] However, it was the subsequent discovery of MAdCAM-1, found exclusively on HEVs within Peyer's patches and also within the lamina propria of the gut, and its ligands, α4β7 integrin and L-selectin, that was a major advance.[99-101] Animals deficient in β7 integrins have markedly impaired abilities to mobilize T cells to the gastrointestinal tract and Peyer's patches.[102] This is probably due only in part to the absence of α4β7 integrins because another β7 integrin, αEβ7 integrin, found on so-called intraepithelial lymphocytes, is involved in T-cell binding to E-cadherin expressed on intestinal epithelium.[103,104]

The α4β7 integrin is broadly expressed in a pattern similar to that for α4β1 integrin (VLA-4) in that it is expressed by all leukocytes except neutrophils.[105] This suggested that there must be additional pathways for recruitment of cells bearing either α4β1 integrins or α4β7 integrins. It is now believed that these additional pathways involve chemokines. For example, the chemokine SLC, a ligand for CCR7, stimulates α4β7 integrin-mediated adhesion of lymphocytes to MAdCAM-1 in vitro.[28] SLC has been detected in gut tissues,[49] and defects in CCR7 or SLC production give rise to mice with markedly reduced numbers of T cells in secondary lymphoid organs, including Peyer's patches.[55,106] The chemokine BLC is important for B-cell accumulation in secondary lymphoid organs, and mice deficient in the BLC receptor CXCR5 fail to develop normal Peyer's

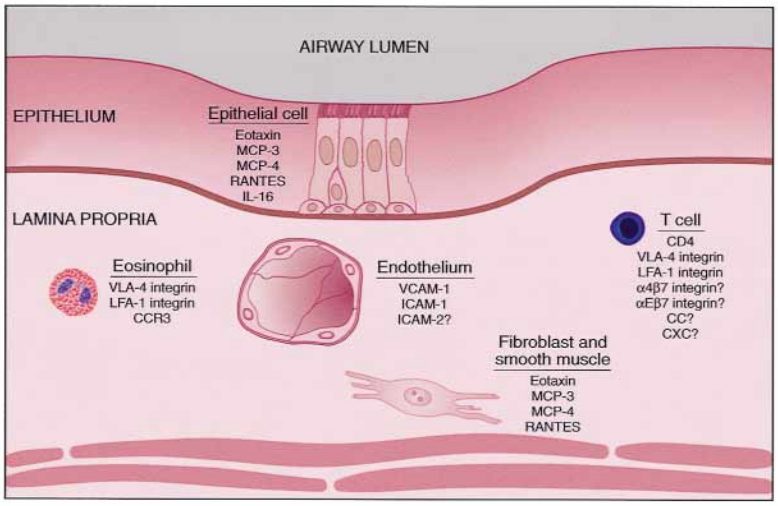

FIG 4. Potential role of adhesion molecules, chemotactic cytokines, chemokines, and chemokine receptors in the accumulation of eosinophils and lymphocytes during T_H2-type inflammatory responses in the lung. Accumulation of lymphocytes in the lung probably involves initial interactions via ICAM-1/LFA-1 integrin and VCAM-1/VLA-4 integrin. A subset of the lung T cells also express αEβ7 integrin and α4β7 integrin, but unlike their well-defined role in gut homing, their role in lung homing is unclear. Although IL-16 (via CD4) may contribute to T-cell accumulation, the chemokines and chemokine receptors involved remain unknown. For eosinophils, interactions implicated in their accumulation in pulmonary tissues include ICAM-1/LFA-1 integrin, ICAM-2/LFA-1 integrin, and VCAM-1/VLA-4 integrin, presumably influenced by eotaxin and other CCR3-active chemokines produced by tissue-resident cells such as respiratory epithelial cells, fibroblasts, and smooth muscle cells.

patches.[57] However, as mentioned above, their expression is not restricted to the gut, so these two chemokines are likely important for lymph node homing in general. Another chemokine, TECK, is produced by the small intestine and also by intestinal epithelial cells but not in skin or lymph nodes.[107,108] TECK is also felt to play an important if not major role within the thymus during T-cell maturation.[108] Its receptor, CCR9, is found on memory $CD4^+$ T cells, especially those expressing high levels of α4β7 integrin, consistent with their predilection for homing to the gut. There is a lack of CCR9 on other memory $CD4^+$ T cells including the CLA^+ skin-homing subset.[109,110] Besides CCR7 and CCR9, other chemokine receptors may be involved in gut mucosal homing. An examination of normal small intestinal tissues obtained from gastric bypass surgeries revealed expression of CCR5 and CXCR3 (receptors normally associated with T_H1 responses, see Table I) on essentially all intraepithelial and lamina propria lymphocytes, and chemokine ligands for these receptors are increased in inflammatory bowel disease.[111]

With respect to eosinophil accumulation in the gastrointestinal tract, these cells possess a similar pattern of adhesion molecules as do gut homing lymphocytes, with the exception of the absence of αEβ7.[75] In murine models of allergic peritonitis, P-selectin, ICAM-1, and VCAM-1 have each been shown to contribute to eosinophil recruitment.[112,113] In contrast to the similar use of adhesion molecules, none of the chemokine receptors implicated in gut homing of T lymphocytes are expressed by human eosinophils.[78,114] As was mentioned above for skin homing, CCR3-active chemokines appear to provide the pathway for eosinophil accumulation. Eotaxin-deficient mice have very few, if any, eosinophils within the villae of the intestine.[115,116] Within the lamina propria of the gastrointestinal tract, eotaxin is produced by mononuclear cells and others, and it appears to be critical for the development of gastrointestinal eosinophilia in orally challenged, food-sensitive mice.[117] However, other than a human duodenal biopsy study of milk-sensitive enteropathy linking eosinophil degranulation to VCAM-1 expression,[118] there are few reports analyzing tissue eosinophilia, adhesion molecules, or CCR3-active chemokines in human intestinal disorders.

Lung homing

Compared with skin, gut, and lymph node homing, the role of adhesion molecules and chemokines in lymphocyte and eosinophil recruitment to the airways is less clear. Part of the difficulty is that human lungs do not normally contain secondary lymphoid organs, so-called BALT (bronchus-associated lymphoid tissue), that is seen in other mammals.[119-122] Therefore it may be misleading to extrapolate to humans results from studies examining leukocyte trafficking to lungs in animals that do contain BALT, such as rabbits, rats, and mice.[120] With this caveat, this section will review information on adhesion molecules and chemokines in allergic inflammation in mechanistic animal models, as well as correlative studies in humans (Fig 4).

With respect to adhesion molecules, studies with knockout mice and adhesion molecule blocking reagents

in various mammals suggest that both ICAM-1 and VCAM-1 (as well as their integrin ligands) are critically important for both eosinophil and T-cell recruitment after allergen exposure, whereas P-selectin, E-selectin, and L-selectin individually appear to be less important or not important at all.[10,123] However, simultaneous inhibition of multiple selectins can lead to significant effects on cell accumulation in the lung.[124] Increased levels of VCAM-1 and ICAM-1 have been detected in human airways in asthma and after experimental allergen challenge.[17,125] Patients with severe forms of leukocyte adhesion deficiency type I often have recurrent pneumonias, whereas those with type II disease do not.[69,98] Other adhesion molecules implicated in eosinophil accumulation in knockout models include CD34 and ICAM-2, although their roles are less apparent.[126,127] Based particularly on the VCAM-1/VLA-4 pathway, efforts to generate specific antagonists are quite advanced, and several clinical trials are under way or planned in asthma.[123,128,129]

With respect to the adhesion phenotype of "lung homing" lymphocytes, it has been shown that the majority of T cells in the airways are $CD4^+$ and $CD45RO^+$, and some express $\alpha4\beta7$ integrin, VLA-1 and the intraepithelial lymphocyte marker $\alpha E\beta7$ integrin, although the latter is found more commonly on lung $CD8^+$ cells.[130-132] They do not express the skin-homing structure CLA, and MAdCAM-1 has never been detected in pulmonary tissues.[66,101] Intraepithelial lymphocytes are observed in normal and inflamed airways, and based on studies of explanted human bronchial tissue into SCID mice, these cells appear to be long lived.[133,134] However, the importance of $\alpha E\beta7$ integrin in lung homing has been seriously questioned by the finding that mice deficient in αE integrins have normal numbers of lung T cells.[104,134] Although it has been proposed that CCR3 may be important for recruitment of T_H2 cells,[135] studies of allergic inflammation in human airways have failed to support this notion.[136] Additional studies performed after endobronchial allergen challenge yielded similar negative results (Bolos, Liu, and Bochner, unpublished observations). Another proposed pathway for T-cell recruitment to the lung involves the epithelial-derived cytokine IL-16, acting through its receptor CD4.[137-139] However, because T_H2 cells get recruited to the lung in asthma, it will be important to determine whether they selectively express the other chemokine receptors associated with T_H2 cells (CCR4 and CCR8) and whether chemokines active on these receptors (MDC and TARC versus I-309, respectively) are produced within the allergic or asthmatic lung.

Eosinophil accumulation during allergic diseases of the airways, including asthma, appears to be mediated by an array of chemokines that are virtually identical to those proposed for other tissues. This makes CCR3 an attractive target for therapeutic intervention in allergic inflammation.[129] Methods including analysis of sputum, bronchoalveolar lavage, and biopsies suggest possible roles for many of these CCR3-active chemokines, including eotaxin, RANTES, MCP-3, and MCP-4.[2,140-142] Given the pronounced ability of respiratory epithelium to produce these chemokines after exposure to T_H2 cytokines, especially in conjunction with TNF,[2,143-146] their role in selective recruitment of eosinophils is strongly suggested. Other lung-resident cells capable of producing these same chemokines include fibroblasts and smooth muscle.[9,141] In contrast, exposure to the cytokine IFN-γ is particularly effective at inducing epithelial production of a different set of chemokines (IP-10, Mig, and I-TAC) active on the T_H1-associated chemokine receptor CXCR3 (Table I), and IP-10 is increased in the airways in patients with tuberculosis, a T_H1 disease.[147] In addition to CCR3-active chemokines, others implicated in animal models of asthma include MDC, MCP-5, MCP-1, and SDF-1.[148-150] Another issue to emerge from murine studies is the possibility that airway eosinophils can reenter the lung parenchyma and migrate to regional lymph nodes in a CCR3-independent manner and, once there, could participate as antigen-presenting cells.[151] Verification of this unusual CCR3-independent pathway is needed.

CONCLUSION

Intricacies of the inflammation superhighway are beginning to be understood. It appears that the immune system has evolved clever mechanisms for controlling leukocyte accumulation during inflammatory responses. Many tissues have been designed with unique patterns of roads (adhesion molecules) with street signs and traffic signals (chemokines) to direct subsets of leukocytes by selective interactions mediated by adhesion ligands and chemokine receptors. This new knowledge gives additional importance to the role played by tissue resident cells, such as endothelium, epithelium, and dendritic cells, in orchestrating the cellular makeup of inflammatory infiltrates. Hopefully the discovery of these selective recruitment pathways will continue to fuel interest in this exciting area and promote the development of novel, tissue-specific anti-inflammatory therapies.

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