

Migration of helper T-lymphocyte subsets into inflamed tissues

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The localization of lymphocytes to specific tissues is a finely regulated event that has key implications in the development of chronic allergic inflammation that is associated with allergic rhinitis, atopic dermatitis, and asthma. Key players in the tissue localization of lymphocytes and other allergic effector cells include cellular adhesion molecules and chemokines. The expression or activation pattern of these proinflammatory mediators appears to depend, in part, on the local cytokine milieu. For instance, the T_H1 phenotype is associated with the upregulation of intercellular adhesion molecule-1 and RANTES, whereas the T_H2 phenotype is associated with the upregulation of vascular cell adhesion molecule and P-selectin. Notably, the recruitment of certain cell populations, such as eosinophils (hallmark of chronic allergic inflammation), into inflamed tissue sites is dependent on the preferential expression of adhesion molecules, chemokines, and associated receptors. The potential mechanisms that underlie cell migration into inflamed tissue as currently understood are reviewed. (*J Allergy Clin Immunol* 2000;106:S264-9.)

Key words: Adhesion molecule, allergic inflammation, chemokine, lymphocyte, T cell, T_H cell

The localization of lymphocytes to tissue during immune/inflammatory responses involves a series of complex mechanisms that include activation of integrin binding, adhesion molecule expression, and tissue-based chemokine production.¹⁻³ The regulation of specific molecules and the expression of particular receptors on lymphocytes during the progression of disease determine the type of T lymphocytes (ie, T_H1 or T_H2 cells) that migrate into the tissue. Although studies have identified and characterized tissue-specific expression of certain adhesion and chemotactic molecules, a more logical view may be that the type of immune/inflammatory response dictates the specific mediators that are expressed.

Although the trafficking of naïve lymphocytes from the blood to lymph nodes is pivotal to the maintenance of effective immune surveillance, the deciphering of the mechanisms involved in lymphocyte recruitment during inflammation may be more pharmaceutically attractive. Functional diversity of T cells has been demonstrated by the observation that naïve T lymphocytes are activated and

Abbreviations used

CCR:	CC chemokine receptor
CxCR:	CxC chemokine receptor
ICAM:	Intercellular adhesion molecule
IP:	IFN- γ inducible protein
MAdCAM:	Mucosal addressin cell adhesion molecule
MCP:	Monocyte chemoattractant protein
MDC:	Macrophage-derived chemokine
MIP:	Macrophage-inflammatory protein
RANTES:	Regulated on activation, normal T-cell expressed and secreted
STAT:	Signal transducers and activators of transcription
TARC:	Thymus and activation-regulated chemokine
TCA:	T-cell activation gene
VCAM:	Vascular cell adhesion molecule

differentiated into naïve T_H0 cells that produce different combinations of cytokines.⁴⁻⁶ Subsequently, depending on the cytokine environment to which the T_H0 cells are exposed, these cells can further differentiate into either T_H1 cells, which synthesize IL-2 and IFN- γ , or T_H2 cells, which synthesize IL-4, IL-5, and IL-13. Over the years, it has become clear that certain diseases are associated with a particular helper T cytokine phenotype. For instance, allergic responses and asthma are largely mediated by T_H2 cells. This review outlines our current understanding of how and why certain helper T-lymphocyte subsets (ie, T_H1 vs T_H2 cells) migrate into inflamed tissues.

ADHESION MOLECULE EXPRESSION IN ALLERGIC INFLAMMATION

One of the initial and most important steps in tissue lymphocyte accumulation is the upregulation of adhesion molecules (eg, E-selectin) on the vascular endothelium.⁷⁻¹⁰ Allergic mediators of the early response (eg, histamine) can rapidly increase the expression of E- and P-selectin molecules on the endothelial surface,¹¹ thereby promoting a reduction in the rolling velocity of circulating lymphocytes in a reversible adhesion event. Subsequently, a second family of adhesion molecules, including intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, are upregulated. These adhesion molecules promote a relatively firm adhesion of the rolling lymphocytes and allow them to spread along the activated endothelium. The firmly adhered lymphocytes are then pulled into the tissue through a complex series of events that involve chemotactic gradients and

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additional adhesion steps. Although the exact mechanisms for cellular recruitment into tissues are still being investigated, cellular adhesion is the primary and therefore possibly the most critical event associated with leukocyte tissue extravasation.

In some cases the type of immune response appears to dictate the selective activation of adhesion molecules. For instance, selectin and ICAM-1 molecules can be induced by acute mediators and T_H1 cytokines. Therefore, these adhesion molecules would be expected to play a larger role in responses that are associated with neutrophil and mononuclear cell populations.⁸ In contrast, VCAM-1 can be preferentially upregulated by T_H2 cytokines (eg, IL-4, IL-13) and may therefore be more closely associated with T_H2 responses.^{12,13} Several studies have demonstrated that the expression of VCAM-1 is associated with allergic inflammation and the localization and recruitment of associated cell populations, especially eosinophils.^{14,15} Thus, there may be a certain profile of adhesion molecule expression that is linked to the phenotype of the developing immune response.

The role of selectins in T-lymphocyte migration in inflammatory skin diseases has been thoroughly investigated. Studies initially found that cutaneous leukocyte-associated antigen-positive T lymphocytes preferentially migrate to the skin.¹⁶⁻¹⁸ Cutaneous leukocyte-associated antigen binds to selectins on activated endothelium.¹⁹⁻²¹ The migration of certain lymphocyte subsets (ie, T_H1 or T_H2) into inflamed skin and the associated pattern of adhesion molecule expression have also been examined. The ability of T_H1 , but not T_H2 , cells to bind selectin molecules may define an important mechanism for the preferential migration of these cells into infected tissue. Because T_H1 cytokines induce selectin molecule expression on the endothelium, and T_H2 cytokines downregulate selectin expression, it stands to reason that T_H1 lymphocytes preferentially migrate under these conditions. Thus, the preferential recruitment of T lymphocytes to the skin appears to depend on a specific adhesion interaction. Further, studies conducted in selectin-deficient mice lend further support of this concept. In those studies, in the absence of selectin, the migration of T lymphocytes into the allergic skin sites was significantly reduced.²²⁻²⁵

A number of studies have also been conducted to examine whether adhesion molecule expression during inflammation is tissue specific. This idea, although initially appealing for certain diseases, may not be the case. However, some adhesion molecules play a more prominent role than others in certain tissues during disease. For example, mucosal addressin cell adhesion molecule (MAdCAM)-1 was originally identified in inflamed bowel diseases. Although recent studies have identified MAdCAM-1 in other tissues, its association with severe inflammatory bowel conditions is the strongest.²⁶⁻³⁰ Recent research has identified MAdCAM-1 as a potential therapeutic target in inflamed bowel disorders. The expression and function of MAdCAM-1 in other tissues are only now under investigation.³¹⁻³³ Nevertheless, the

function of MAdCAM-1 in the intestinal tract demonstrates one area in which a particular adhesion molecule predominates. The $\beta7$ -integrin that binds to MAdCAM-1 is $\alpha4/\beta7$. The $\beta7$ -integrin(+) T lymphocytes appear to specifically migrate to the intestinal tract, not only binding to MAdCAM-1 but also to other adhesion molecules, such as e-cadherin. Thus, the specificity of the lymphocyte homing to the gut is determined by a combination of local adhesion molecules expressed in the tissue and the $\beta7$ integrin on the lymphocyte.

CHEMOKINE AND CHEMOKINE RECEPTOR PATTERNS DURING T LYMPHOCYTE RESPONSES

Although adhesion molecule expression is fundamental in the localization of leukocytes to inflamed tissue, adhesion molecules are only partially responsible for the preferential recruitment of specific leukocyte subsets during certain diseases. The migration of lymphocytes into tissues appears to depend on the expression of specific chemokines during the progression of the inflammatory disease. Chemokines are a family of small molecular weight cytokines that are important for localization of particular leukocyte populations during immune/inflammatory responses.^{1,34-38} Chemokines are primarily divided into 2 main groups (CxC and CC), based on the juxtaposition of the first 2 cysteine residues in the amino acid sequence (Table I). The responses induced by chemokines are initiated by way of specific G-protein-coupled receptors on the cell surface. Although not entirely characterized, it appears that there are no less than 5 different CxC family receptors and 10 different CC family receptors. Members of the CC chemokine subfamily have been implicated as potential mediators of allergic inflammation because of the ability to induce migration of eosinophils, T cells, and monocytes. Eosinophilia is a hallmark of allergic inflammation that is associated with allergic rhinitis, atopic dermatitis, sinusitis, and asthma. In addition to playing a prominent role in the tissue localization of leukocytes, these activating factors are also involved in important biologic events, such as eosinophil and mast cell degranulation, differentiation of helper-T-lymphocyte phenotypes, and the regulation of antibody isotype switching.^{3,39-41} Thus, these molecules have important functions in multiple phases of the developing immune response.

The initial studies of chemokine biologic factors defined the role of early response cytokines (ie, cytokines released after mast cell degranulation), such as tumor necrosis factor and IL-1, in chemokine activation. These early studies demonstrated that cytokines could induce chemokine expression in nearly every cell type. Subsequently, investigators have begun to define the association of certain chemokine profiles with particular types or phases of immune responses. In fact, the preferential expression of certain chemokines during immune responses likely dictates their function. For example, the CC chemokine family members (RANTES, and

TABLE I. Chemokine receptors and associated ligands

Chemokine receptors	Ligands
CxC	
CxCR1	IL-8, GCP-2
CxCR2	IL-8, GCP-2, GRO α , GRO β , GRO γ , ENA-78
CxCR3	IP-10, Mig, ITAC
CxCR4	SDF-1
CxCR5	BLC-1
CC*	
CCR1	MIP-1 α , MIP- δ , RANTES, HCC-1, MCP-3
CCR2	MCP-1 to MCP-5
CCR3	Eotaxin, eotaxin-2, MCP-3, MCP-4, RANTES
CCR4	TARC, MDC
CCR5	MIP-1 α , MIP-1 β , RANTES
CCR6	MIP-3 α
CCR7	SLC, MIP-3 β
CCR8	I-309, TARC, MIP-1 β
CCR9	MIP-1 α , MIP-1 β , MCP-1, MCP-5
CCR10	TECK, SLC, MIP-3 α , BLC-1

GCP, Granulocyte chemotactic protein; GRO, growth-regulated oncogene; ENA, epithelial-derived neutrophil attractant; Mig, monokine-induced by interferon- γ ; ITAC, interferon-stimulated T-cell α chemoattractant; SDF, stromal cell-derived factor; BLC, B-lymphocyte chemoattractant; HCC, human CC chemokine; SLC, secondary lymphoid tissue chemokine; TECK, thymus-expressed chemokine.

*CC chemokines with unknown receptors: PARC, HCC-2, HCC-3, HCC-4, CCF-18.

macrophage-inflammatory protein [MIP]-1 α) are induced by IFN- γ and tumor necrosis factor. Further, the production of these chemokines, although regulated by IL-4 (a T_H2 cytokine), appears to be closely associated with T_H1 responses.⁴² Likewise, the production of CxC chemokine receptor (CxCR)3 ligands (IFN- γ inducible protein-10 [IP-10], monokine-induced by IFN- γ , and IFN-stimulated T-cell α chemoattractant) are specifically activated by interferon and may have critical roles in enhancing T_H1 lymphocyte recruitment and activation.^{43,44} In addition to preferential expression of chemokines during T_H1 responses, preferential expression of the associated chemokine receptors on T_H1 lymphocytes has been reported. A number of studies have demonstrated the preferential expression of CC chemokine receptor 1 (CCR1), CCR5 (which binds RANTES and MIP-1 α), and CxCR3 (which binds IP-10, monokine-induced by IFN- γ , and interferon-stimulated T-cell α chemoattractant) on T_H1 lymphocytes.⁴⁵⁻⁴⁷ Thus, chemokine expression during a T_H1 response correlates directly with the specificity of the chemokine receptors expressed on T_H1 lymphocytes.

In addition to select chemokines associated with T_H1 responses, certain chemokines are closely associated with T_H2 responses. An extensive amount of work has been performed on CC chemokines, with the finding that particular members of this family are specifically activated by IL-4 and IL-13 (T_H2 phenotype).⁴⁸⁻⁵³ The CC chemokines preferentially upregulated by T_H2, but not T_H1, cytokines, include monocyte chemoattractant protein-1 (MCP-1), eotaxin, T-cell activation gene 3

(TCA3), thymus and activation-regulated chemokine (TARC), and macrophage-derived chemokine (MDC). Interestingly, chemokines induced by IL-4 and IL-13 bind to a single chemokine receptor (Table I). This is unusual among chemokines because they tend to exhibit a promiscuous binding pattern and interact with multiple chemokine receptors.

The T_H2 cytokines and associated chemokines are particularly important in allergic inflammation. Studies have indicated that MCP-1 is involved in allergen-induced T-lymphocyte accumulation in the lungs of sensitized mice, whereas eotaxin is most closely associated with eosinophil accumulation during allergic responses.⁵⁴⁻⁵⁶ Thus, the T_H2 activation pathway, which has been associated with allergen-induced airway hyperreactivity, likely induces chemokines that are associated with allergic cell recruitment. This area will be of particular interest because studies have previously demonstrated that T_H2-associated chemokines play significant roles in allergen-induced airway inflammation and airway hyperreactivity.⁵⁶⁻⁶²

In vitro studies of T_H2 cells indicate that they preferentially express CCR3 (eotaxin), CCR4 (MDC, TARC), and CCR8 (TCA3).^{45,46,63} This receptor expression pattern correlates well with the type of chemokines that are induced by T_H2 responses. Importantly, a recent study by Lloyd et al⁶⁴ demonstrated that both CCR3 and CCR4 are used for sequential movement of T_H2 cells into allergen-challenged lungs. In addition to lymphocyte migration, there is preferential chemokine receptor expression on effector cells (eg, eosinophils, basophils) known to migrate into and damage the airway, leading to airway hyperreactivity. Both eosinophils and basophils have been shown to express a preferential pattern of chemokine receptors. Eosinophils primarily express CCR3 (eotaxin receptor), whereas basophils express both CCR2 (MCP-1 receptor) and CCR3.⁶⁵⁻⁶⁹ Overall, the recruitment of multiple cell populations into allergic tissues is mediated by a combination of preferential chemokine production within the inflamed tissue and the selective expression of chemokine receptors on marginated leukocyte populations.

CHEMOKINE PRODUCTION IS REGULATED BY STAT6

Signal transduction and activation pathways common in many cell populations may specifically regulate the determination of preferential chemokine production and receptor expression. The activation of specific T_H responses is regulated by intracellular signal pathways that include signal transducers and activators of transcription (STAT) protein activation.⁷⁰ Specific cytokine ligand binding to cytokine receptors can activate STAT protein pathways. For example, IL-12 has been shown to specifically activate cells through STAT4, whereas IL-4 and IL-13 activate cells through STAT6.⁷⁰ Thus, T_H1 or T_H2 cytokines produced during an immune/inflammatory response may induce a preferential profile of chemokines through a specific signaling mechanism.⁴⁹

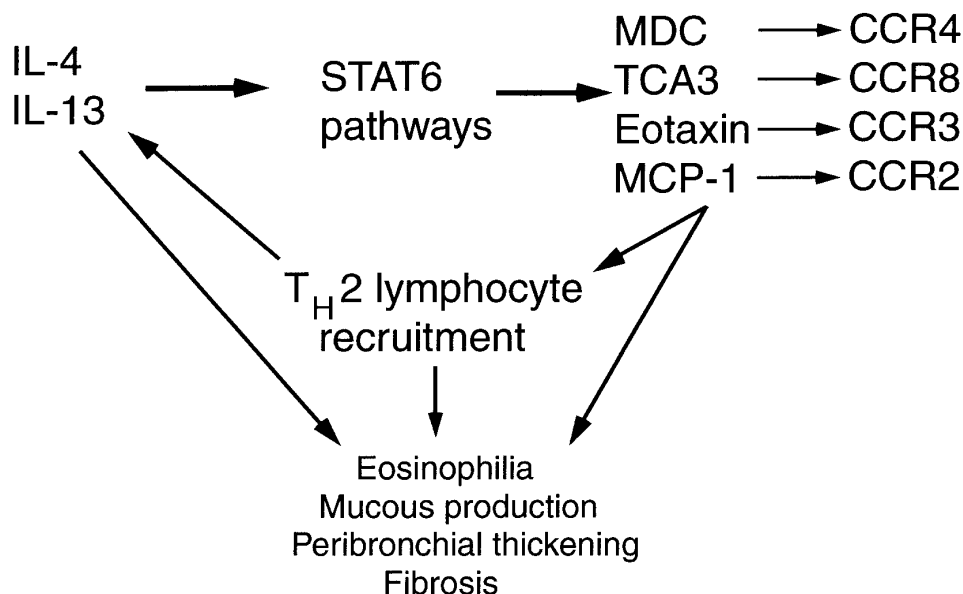


FIG 1. Cytokine networks in T_H2 lymphocyte migration. T_H2 cytokines induce the production of specific chemokines through STAT6 activation pathways, which leads to the recruitment of T_H2 lymphocytes and eosinophils. The continued activation of these cell populations promotes the chronic pathophysiologic dysfunction observed during asthma (including mucous production, peribronchial thickening, and fibrosis). These pathways may be initiated and maintained through chronic allergen exposure.

TABLE II. STAT6 regulates CC chemokine production from T_H cells

Chemokines	Relative expression of chemokines			
	T_H1	T_H2	T_H1 (STAT4 $-/-$)	T_H2 (STAT6 $-/-$)
MIP-1 α	++	++	++	++
MIP-1 β	++	++	++	++
RANTES	++	–	++	+++
Lymphotactin	++	–	++	+++
MDC	–	+++	–	–
TCA3	–	+++	–	–

To investigate the specific role of STAT proteins, experiments were conducted on lymphocytes derived from either STAT4 or STAT6 “knockout” ($-/-$) animals (unpublished data). Short-term T-cell lines were created from the spleens of control and STAT $-/-$ animals and skewed to either a T_H1 or T_H2 phenotype with standardized protocols of differentiation. Once skewed, the cells were restimulated with anti-CD3/anti-CD28, and the chemokine profiles were examined. The data indicated that T_H1 -skewed cultures preferentially produced RANTES and lymphotactin, whereas T_H2 -skewed cultures preferentially produced MDC and TCA3 (Table II). These results were consistent with previous investigations that demonstrated preferential expression of chemokines during specific T_H -type responses.^{71,72} When these experiments were performed in parallel with lymphocytes from STAT4 $-/-$ and STAT6 $-/-$ mice, the results were surprising. Even though STAT4 regulates T_H1 -cell development, the lymphocytes from STAT4 $-/-$

mice demonstrated no alteration in chemokine profile. However, the lymphocytes from the STAT6 $-/-$ mice showed that RANTES and lymphotactin were significantly upregulated, whereas MDC and TCA3 were downregulated. Thus, the determination of which chemokine is produced by CD4⁺ T lymphocytes is dictated by whether STAT6 is induced. These results correlated well with the type of chemokines that are produced in T_H1 versus T_H2 cell responses. It would be interesting to determine whether chemokine receptors on lymphocytes and chemokines from other cell populations follow similar regulatory pathways.

SUMMARY

The localization of lymphocytes to specific tissues is a finely regulated event that involves several complex mechanisms. The local activation of vascular endothelium and the upregulation of specific adhesion molecules

comprise the initial phase of the inflammatory process. After adhering to the activated endothelium, lymphocytes subsequently migrate based on the chemokines expressed within the tissues and the chemokine receptors expressed on the lymphocytes (Fig 1). With respect to T_H2 responses, STAT6 (IL-4/IL-13 dependent) is emerging as an important activational pathway for the expression of specific tissue chemokines. These chemokines have been shown to exert specific functions on T_H2 lymphocyte and effector cells (basophil and eosinophil), including recruitment and activation, and in so doing, play a central role in promoting allergic inflammatory responses. Overall, the T_H2 cytokines in conjunction with specific expression of chemokines and chemokine receptors initiate and maintain the intensity of chronic inflammation observed in allergic disease.

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