

T Cell Trafficking in Allergic Asthma: The Ins and Outs

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Key Words

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Abstract

T cells are critical mediators of the allergic airway inflammation seen in asthma. Pathogenic allergen-specific T cells are generated in regional lymph nodes and are then recruited into the airway by chemoattractants produced by the asthmatic lung. These recruited effector T cells and their products then mediate the cardinal features of asthma: airway eosinophilia, mucus hypersecretion, and airway hyperreactivity. There has been considerable progress in delineating the molecular mechanisms that control T cell trafficking into peripheral tissue, including the asthmatic lung. In this review, we summarize these advances and formulate them into a working model that proposes that T cell trafficking into and out of the allergic lung is controlled by several discrete regulatory pathways that involve the collaboration of innate and acquired immune cells.

Airway hyperresponsiveness

(AHR): increase in narrowing of airways from airway smooth muscle hypercontraction in response to stimuli such as histamine or allergen exposure

Mucus hypersecretion:

tendency of the mucus-secreting cells in the airway lining of asthmatics to hypertrophy and increase mucus secretion

DC: dendritic cell

INTRODUCTION

Asthma is a complex syndrome broadly defined by inflammation of the airways associated with airway hyperresponsiveness (AHR) and mucus hypersecretion (1). Asthma has a prevalence estimated at 5% of the population, making it one of the most common chronic diseases worldwide (2). Despite effective therapies, the incidence of this disease and the frequency of its significant complications are increasing. New therapeutic approaches based on our understanding of the pathophysiology of asthma could have profound repercussions for the care of asthmatics and the health of the public in general.

T lymphocytes are important mediators of adaptive immune responses and are vital for host defense against infection. The lung has a large network of antigen-presenting cells and lymphatics that aid in antigen presentation to T cells in associated lymphoid tissue located within the lung parenchyma and mediastinum. In addition, the adult lung contains T cells (the majority of which are memory cells) residing in the alveoli, airway (bronchial) lumen, intraepithelial layer, submucosa, and interstitium (3). Although important for immunity, aberrant accumulation of T cells in the lung is seen in numerous noninfectious pulmonary inflammatory diseases such as asthma, where T lymphocytes in the lung are believed to orchestrate an abnormal inflammatory process (4, 5). In asthma, the airways develop prominent inflammation with accumulation of activated effector T cells around the airways and in the airway lumen. It is thought that these cells are recruited into the lung and serve as the critical controllers of airway inflammation. In this review, we explore the mechanisms of T cell homing into the lung during asthma and present a paradigm for the mechanisms that control the movement of these cells into and out of the airways.

ASTHMA PATHOGENESIS

The hallmark of asthma is chronic airway inflammation associated with reversible air-

way dysfunction. This causes the classic symptoms and signs of asthma: shortness of breath, cough, mucus production, and wheezing. Although there is a growing recognition that the type of inflammation in the airways can be heterogeneous (6), in most cases the airway inflammation characteristic of asthma results from an allergic-type reaction to an inhaled antigen from the environment (so-called allergic asthma). In allergic asthma, the airways develop predominantly eosinophilic inflammation with prominent edema and mucus production in response to inhalation of antigen. In addition, smooth muscle cells of the airways become hyperreactive, leading to reversible bronchoconstriction in response to various stimuli. In nonallergic asthma, neutrophilic and pauci-immune forms have been described, but it is unclear if these represent distinct clinical phenotypes, as they often respond to conventional asthma therapy (6). In addition, the role of T cells in nonallergic (or noneosinophilic) asthma is currently unknown. For these reasons, in this review, we focus on the homing of T cells only in the allergic form of asthma.

Sensitization

One of the earliest steps in the establishment of allergic sensitization to an antigen is the generation of an antigen-specific T cell response (**Figure 1a**). Antigens from the environment are constantly introduced into the airways with every breath. Multitudes of airway DCs (dendritic cells) are located under the airway epithelium, where they form an antigen-sampling network in the airway mucosa (7–9). It is thought that adjuvant signals from airway epithelium such as TSLP (thymic stromal lymphopoietin) and GM-CSF (granulocyte-macrophage colony-stimulating factor), generated in response to inhaled stimuli, influence the activation/maturation state of DCs and help determine whether a particular allergen will trigger a Th2-type inflammatory response or will lead to tolerance (5, 8, 10–12). Once DCs mature

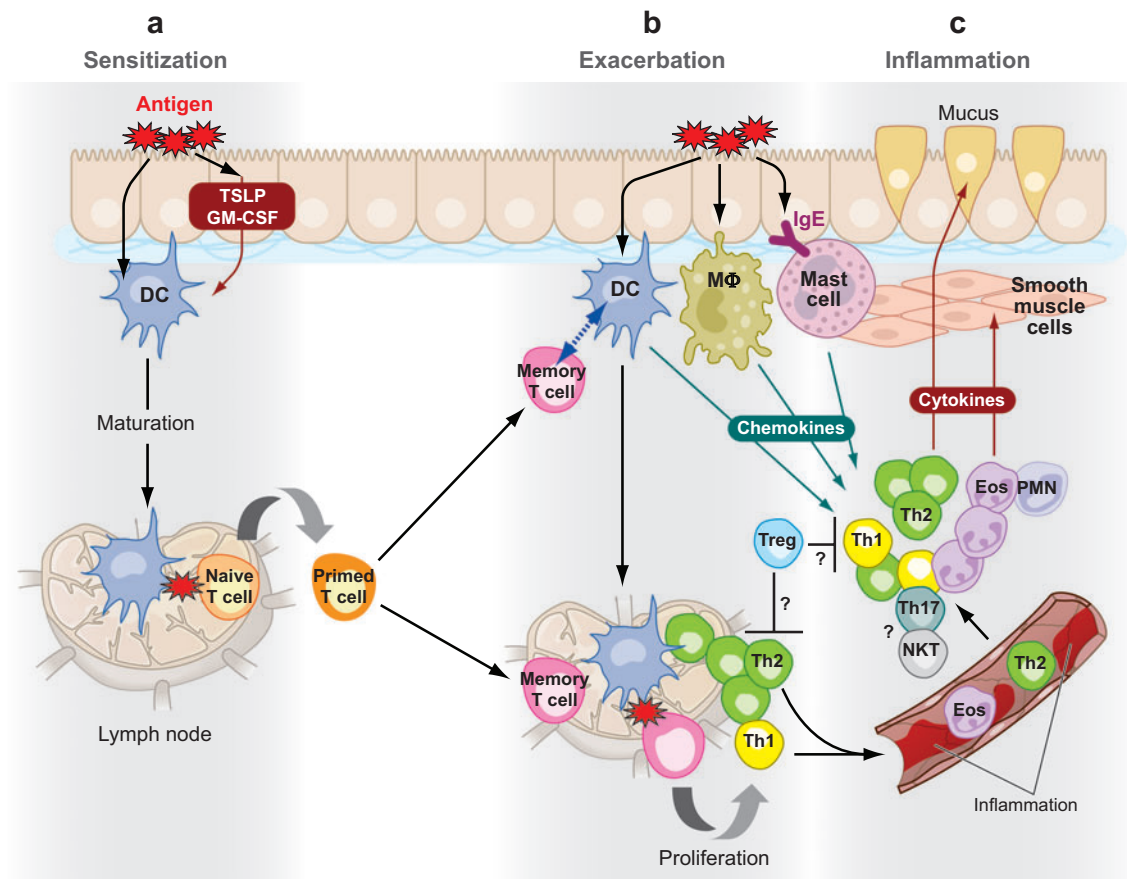


Figure 1

Asthma pathogenesis. (a) Sensitization to an allergen results from uptake by airway dendritic cells (DCs), maturation of the DCs, migration to lymphoid tissue, and antigen presentation to T cells. Maturation of the DCs requires secondary stimuli generated from epithelial cells following antigen exposure. These primed T cells then reenter the lung, where they provide surveillance for the allergen. (b) Exacerbation of allergic airway inflammation occurs when there is reexposure to allergen and uptake by airway DCs with presentation of antigen to airway-associated T cells as well as T cells in lymphoid tissue. T cells in the lymph node then proliferate and home to the lung, where they amplify the airway inflammation. (c) The full allergic airway phenotype results from cytokine production from T cells as well as from inflammatory mediators released from recruited eosinophils and other cells in the lung. This results in mucus hypersecretion, smooth muscle cell hyperreactivity, and airway remodeling with chronic inflammation. (PMN, polymorphonuclear cell; Eos, eosinophil; MΦ, macrophage; Treg, T regulatory cell; NKT, natural killer cell.)

and migrate to the draining lymphoid tissue, they can activate antigen-specific T cells, thus sensitizing the individual to the inhaled antigen. Allergen-specific memory T cells then migrate into the airways where they can reside long term, even during asymptomatic periods (13–16).

Exacerbation

Once an individual is sensitized to an antigen, reexposure in the lung rapidly leads to an exacerbation of allergic airway inflammation (**Figure 1b**). Allergic responses in the airways of sensitized individuals begin with deposition of allergen in the airway mucosa. Once in the

Early asthmatic response (EAR):

initial wave of inflammation, airway edema, and airway narrowing occurs within minutes following allergen exposure. Results predominantly from mast cell degranulation

Late asthmatic response (LAR):

second wave of inflammation and airway narrowing occurs within hours to days. Results largely from T cell-mediated inflammation

Chemokine

receptor: seven-transmembrane G protein-coupled receptor (GPCR) that induces chemotaxis and adhesion in cells after encounter with a cognate chemokine ligand

CRTH2:

chemoattractant receptor-homologous molecule expressed on T helper type 2

LTB₄: leukotriene B₄

PGD₂: prostaglandin D₂

airway, the allergen can react with various innate immune cells and can bind to preformed IgE and IgG antibodies in the airways, leading to immediate mediator release from mast cells and causing the so-called early asthmatic response (EAR). These mediators lead to airway edema and bronchoconstriction and initiate the inflammatory infiltrate. Inhaled allergen is also taken up by the airway DCs, which are then stimulated to mature and migrate to local lymphoid tissue (8). Once in the lymph node, the DCs present processed antigen to both memory and naive T lymphocytes, leading to T cell activation and differentiation. These activated effector T lymphocytes then migrate into the airways, where they secrete cytokines and other mediators, which direct the late asthmatic response (LAR) in the airway.

Asthma Inflammation

In response to cytokines secreted by effector T cells, structural cells as well as other leukocytes in the lung are stimulated to release further inflammatory mediators (**Figure 1c**). This release then stimulates the phenotypic endpoints in asthma: recruitment of eosinophils, mucus hypersecretion by goblet cells in the airway epithelium, smooth muscle cell hyperreactivity, and airway remodeling with chronic inflammation. Eosinophils release further mediators and cytokines into the airways and are critical for the full manifestation of the asthma phenotype (17–20).

RECRUITMENT OF T CELLS INTO THE ASTHMATIC LUNG

After exposure to allergen, the number of T cells in the airways increases dramatically, amplifying allergic inflammation (21, 22). Experiments in animal models have demonstrated that, following allergen challenge, antigen-specific T cells in the airways do not proliferate but are recruited into the lung from regional lymph nodes, leading to the increase in T cells in the airways (23). Allergen-specific naive and memory T cells in the lymph nodes are stimulated to proliferate by antigen-

loaded and -activated DCs that have recently migrated from the airways. Thus, a therapeutic strategy that interrupts the recruitment of pathogenic effector T cells generated in lymphoid tissue from homing to the lung or that enhances the recruitment of regulatory T cells (Tregs) into the lung should effectively interrupt airway inflammation in asthma (24). To accomplish this goal, the molecular mechanisms that regulate T cell homing into and out of the asthmatic lung need to be fully elucidated.

T CELL TRAFFICKING IN THE ALLERGIC ASTHMATIC RESPONSE

Chemokines, Lipid Chemoattractants, and Cognate Receptors

The recruitment of leukocytes into tissue during the asthmatic response is controlled by chemokines and lipid chemoattractants (14, 25). Chemokines (chemotactic cytokines) are 8- to 10-kDa proteins, which are secreted from cells to form a gradient. Chemokines signal through specific cognate chemokine receptors [seven-transmembrane G protein-coupled receptors (GPCRs)] to induce functional responses, such as adhesion and chemotaxis. Engagement of chemokine receptors with cognate chemokine ligand leads to the movement of cells toward the chemokine gradient. In addition to chemokine receptors, subsets of T cells also express specific seven-transmembrane GPCR lipid chemoattractant receptors, including BLT1 and CRTH2, which play important roles in recruitment during the early asthmatic response. Leukotriene B₄ (LTB₄) and prostaglandin D₂ (PGD₂) signal through BLT1 and CRTH2, respectively, to induce chemotactic recruitment of T cells and other leukocytes.

Chemokine-Mediated T Cell Trafficking into Tissue

T cell trafficking is a tightly regulated and complex process that involves expression of

numerous different adhesion molecules and chemokines (26). These signals allow T cells to arrest on endothelial cells and migrate into the tissue. Once in the tissue, further signals generated from chemokine gradients can then guide T cells into specific microcompartments, such as the alveoli or bronchial lumen (3). Thus, the signals that determine the migration and homing of T cells into the lung are crucial for effective immune function. However, inappropriate homing of T cells into the lung may also be a critical component of asthma.

Homeostatic and Organ-Specific Trafficking

Homeostatic and tissue-specific T cell trafficking is required for regulated immune surveillance. Specific chemokine receptors have been associated with T cell homing to tissue-specific sites, including CCR7 and CXCR5 for the lymph node, CCR9 for the small intestine, and CCR4, CCR8, and CCR10 for the skin (27, 28) (**Figure 2**).

It was initially proposed that CD4⁺ T cells could be divided into naive (CD45RA⁺

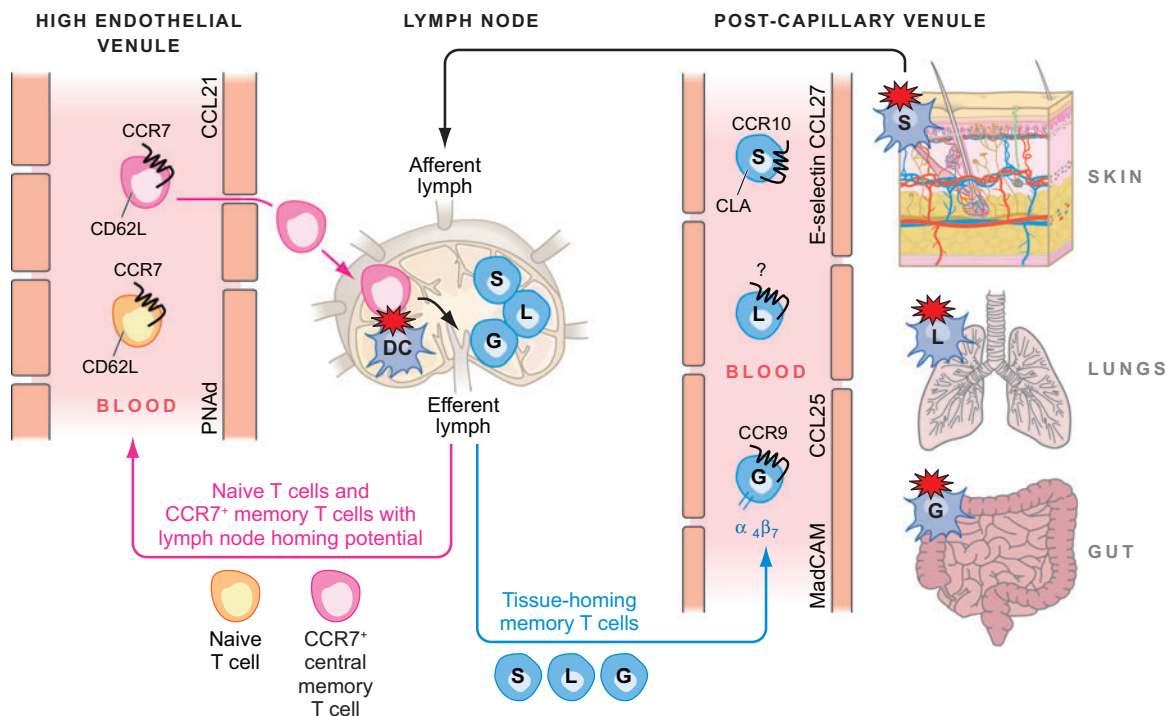


Figure 2

Homeostatic- and organ-specific T cell homing. Specific chemokine receptors have been associated with organ-specific trafficking and recirculation. CCR7 has been associated with T cell homing and recirculation into lymphoid tissue. Initially, it was proposed that “central” memory CCR7⁺ T cells must lose CCR7 expression and gain tissue-specific chemokine receptors in order to home to tissue-specific locations. However, CCR7⁺ memory T cells have been found in the tissue, and it is now believed that CCR7 defines T cells with lymph node-homing potential. In addition, CCR10 is enriched on CLA⁺ skin homing T cells (S), whereas CCR9 is enriched on $\alpha_4\beta_7^{\text{hi}}$ gut (G) homing T cells. These receptors are believed to define T cells with either skin- or gut-homing potential. No such chemoattractant receptor has yet been identified for lung-specific T cell homing (L).

CCR7⁺), central memory (CD45RA⁻ CCR7⁺), and effector memory (CD45RA⁻ CCR7⁻) populations based on CD45RA and CCR7 expression patterns (29). According to this model, naive and central memory T cells express CCR7 and can home to lymph nodes, whereas effector memory T cells must lose expression of CCR7 and gain tissue-specific homing receptors. This model has subsequently been refined by observations that CCR7⁺ T cells are found in tissue sites, including the lung (22, 30–32). We and others have found that CCR7 expression on T cells in the tissue marks T cells capable of recirculation to the lymph nodes (33, 34). CCR7 expression is likely regulated dynamically in vivo and may be responsible for the return of peripheral tissue T cells to the lymph node in the process of antigen surveillance.

Other examples of tissue-specific homing receptors include CCR4, CCR8, and CCR10 for the skin and CCR9 for the small intestine. CCR4, CCR8, and CCR10 expression is associated with CLA⁺ skin-homing T cells, and the cognate ligand for CCR10, CCL27, is highly expressed in the skin at baseline (35). The CCR4 ligand, CCL17, and the CCR8 ligand, CCL1, are also found in the skin, but their pattern of expression is less restricted than that of CCL27 (28, 36–38). Similarly, CCR9 is associated with $\alpha_4\beta_7^{\text{hi}}$ small intestine-homing T cells, and its cognate ligand CCL25 is found in epithelial crypts of the small intestine (39, 40).

Currently, no chemoattractant receptor has been specifically associated with homing to the lung or airways. This suggests that homing to the lung or airway at baseline may require a combination of chemoattractant receptors or that there is an as yet unidentified chemoattractant receptor involved in this process.

Inflammation-Driven Migratory Patterns of Memory T Cells

In addition to this model of homeostatic- and tissue-specific trafficking, T lymphocytes

must be able to respond to sites of inflammation (**Figure 3**). This inflammatory response can lead to control of viral or bacterial infection but can also be dysregulated and lead to an overexuberant response to an allergen in allergic asthma.

In Th2-type inflammation, production of STAT6-inducible chemokines from resident cells at sites of inflammation recruits IL-4-, IL-5-, or IL-13-secreting Th2 cells through the cognate Th2-associated receptors CCR4 and CCR8 (41). This serves to locally amplify Th2-type inflammation. In contrast, in Th1 inflammation, production of STAT1-inducible chemokines from resident cells at sites of inflammation recruits IFN- γ -secreting Th1 and CD8 effector T cells through the cognate chemokine receptors, CCR5, CXCR3, and CXCR6 (42). This serves to locally amplify Th1-type inflammation. Although these receptors have been observed on in vitro polarized T cells, the ex vivo chemoattractant receptor expression pattern is more complex. For example, in human peripheral blood Th1, but not Th2, cells are CXCR3⁺ CCR4⁻, whereas Th2, but only rarely Th1, cells are CXCR3⁻ CCR4⁺ (32). However, the population of CXCR3⁺ CCR4⁺ T cells is a mixture of Th1, Th2, and Th0 cells. This pattern illustrates the important interrelationship of chemokine receptor expression profiles on T cells in vivo.

Th17 inflammation is only beginning to be understood. Because Th17 inflammation is STAT3 inducible, it will be of interest to identify STAT3-inducible chemokines that could be involved in Th17 cell recruitment (43). A recent study has shown that human Th17 cells are enriched in the CCR6⁺ CCR4⁺ subset of CD4⁺ T cells, whereas Th1 cells are enriched in the CCR6⁺ CXCR3⁺ and CCR6⁻ CXCR3⁺ subsets and Th2 cells in the CCR6⁻ CCR4⁺ subset (44). CCR6 is highly enriched on memory T cells and immature, but not mature, DCs (45, 46). The ligand for CCR6, CCL20, is highly expressed on inflamed epithelium, which could bring together memory T and immature DCs in the tissue

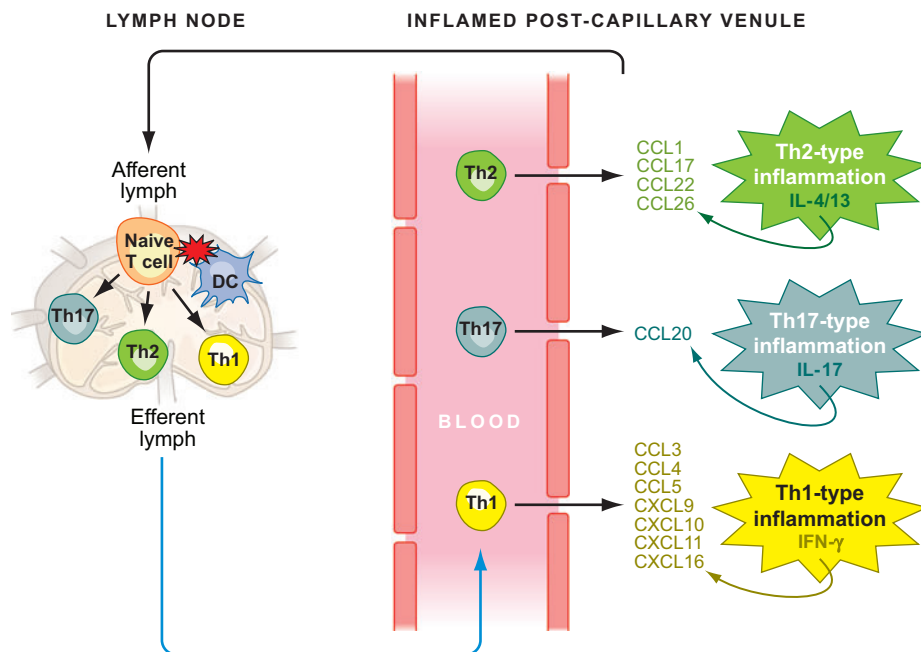


Figure 3

Inflammation-driven migratory patterns of effector T cells. $CD4^+$ T cell-driven inflammation is characterized by the predominant type of cytokines secreted by infiltrating T cells. In Th1-type inflammation, $IFN-\gamma$ predominates; in Th2-type inflammation, IL-4, IL-5, and IL-13 predominate; and in Th17-type inflammation, IL-17 predominates. These cytokines in turn induce specific subsets of $IFN-\gamma$ -inducible chemokines; IL-4- and IL-13-inducible chemokines; or IL-17-inducible chemokines at the site of inflammation. These chemokines then induce the recruitment of T cells that express the specific cognate receptors for these inflammatory chemokines.

(47, 48). Another recent study also identified Th17 cells as enriched in the $CCR2^+ CCR5^-$ subset of $CD4^+$ memory T cells (49). Further studies are required to more fully differentiate chemoattractant receptors on Th17 cells from other subsets of T cells.

In contrast to Th1, Th2, and Th17 cells, Tregs are not responsible for promoting cytokine-induced inflammation but rather for regulating inflammation generated by other T cell subsets. Tregs can traffic as part of immune surveillance homeostatically, but also respond to inflammation-induced chemokine gradients to inhibit overly exuberant T cell responses. It is necessary to understand Treg trafficking patterns in the context of the asthmatic response because these $CD4^+$ T cells

could play an important role in controlling allergic asthma. In mouse models of disease, the chemokine receptors CCR4 and CCR7 play critical roles in Treg trafficking and function in the draining lymph node (50–52), whereas CCR5 is important for Treg trafficking and function at sites of inflammation (53, 54). In addition, CCR8 has been observed on human and mouse $FoxP3^+$ Tregs (52, 55, 56). Tregs likely function in peripheral tissue as well as in draining lymphoid tissue and utilize different sets of chemokine receptors to accomplish these functions. A summary of the key factors for Th1, Th2, Th17, and Treg cell development and the chemokine receptors expressed on these different T cell subsets is shown in **Figure 4**.

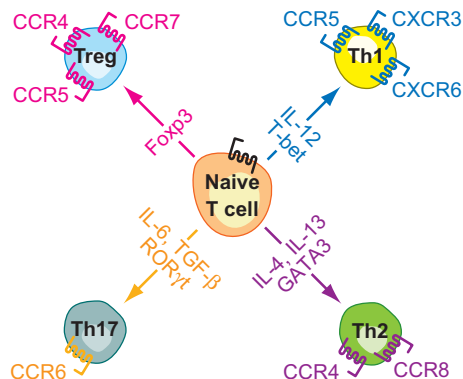


Figure 4

Chemokine receptors and CD4⁺ T cell subsets. Chemokine receptors associated with the differentiation of CD4⁺ T cells under the influence of the indicated cytokines and transcription factors. The pattern of chemokine receptors expressed by a given CD4⁺ T cell subset indicated in the figure does not define that subset nor is it necessarily specific for that subset, but it does dictate the specific homing potential of that specific T cell subset. Although certain chemokine receptors have been associated with a specific CD4⁺ T cell subset, chemokine receptor expression in vivo is complex and overlapping. This expression allows for recruitment of a variety of T cells under inflammatory conditions for immune control.

CD4⁺ T CELL SUBSETS IN THE ALLERGIC ASTHMATIC RESPONSE

Allergic airway inflammation is thought to be mediated by Th2 cells and their cytokines. However, it is also becoming increasingly clear that other subsets of CD4⁺ T cells, such as Th1 (57–59), Th17 (60), Treg (61–63), and CD1d-restricted NKT cells (64, 65), may also play a role in the modulating allergic pulmonary inflammation. Other non-CD4⁺ T cell subsets, such as CD8⁺ T cells and $\gamma\delta$ T cells, are also present in the airway, although at numbers 2-fold and 20-fold less than CD4⁺ T cells, respectively (66). However, the role of CD8⁺ T (67, 68) and $\gamma\delta$ T (69, 70) cells in the asthmatic response is less clear. Therefore, we focus on CD4⁺ T cells in this review.

Th2 Cells

In support of this central role of Th2 cells, levels of Th2-type cytokines, including IL-4, IL-5, and IL-13, were elevated at baseline in the airways of human asthma patients (71, 72). Following segmental allergen challenge, increases in Th2 cytokines have been measured in allergic asthmatic subjects (21, 73–76). In addition, murine models of allergic pulmonary inflammation and AHR have elegantly demonstrated that Th2 cells and the cytokines they secrete were essential for the development of eosinophilia and AHR (77–80). Furthermore, adoptive transfer of effector Th2 cells into naive mice followed by exposure to inhaled antigen induced the pathophysiologic features of asthma, including eosinophilic inflammation, mucus hypersecretion, and AHR (81–83), demonstrating that these cells were fully capable of producing the asthma phenotype. Taken together, these data reveal that Th2 cells and the cytokines they secrete are central to the pathogenesis of asthma.

Although Th2 cells play a critical role in asthma pathogenesis, they are not the predominant T cells in human BAL (bronchoalveolar lavage) from asthmatic subjects, as measured by intracellular cytokine staining (22, 84–86). Following segmental allergen challenge, the total number of IL-4-producing T cells was increased, but the percentage of IL-4 producing Th2 cells was unchanged from prechallenge levels (22, 66, 84). Thus, other T cell subsets must be recruited to the asthmatic BAL along with Th2 cells.

Th1

In addition to Th2 cells, Th1 lymphocytes are also recruited into the lung, where they are capable of either increasing or decreasing the severity of the asthmatic response (57–59). In an adoptive transfer murine model of asthma, it was demonstrated that antigen-specific Th1 cells could suppress Th2-mediated airway

Segmental allergen challenge:

instillation of known allergen into a segment of the lung to induce an in vivo allergic response in sensitized individuals

Bronchoalveolar lavage (BAL):

wash of alveolar and bronchial airspaces using a bronchoscope to instill fluid and retrieve cells and protein secretions

eosinophilia but did not prevent Th2 cell recruitment or eosinophilia in the lung (57). However, other adoptive transfer mouse models have shown that Th1 cells actually enhance Th2 trafficking and airway eosinophilia (58, 59). Additionally, in human subjects, inhaled IFN- γ led to an increase in lymphocyte recruitment to the airway (87).

Following human segmental allergen challenge, the total number of IFN- γ -producing T cells as measured by intracellular cytokine staining increased, but the percentage of IFN- γ Th1 cells decreased somewhat in comparison to prechallenge levels (22, 66, 84). This indicates that Th1 cells traffic to the asthmatic lung, but the decrease in percentage of Th1 cells indicates that these cells may not be preferentially recruited in comparison to other T cell subsets. Th1 cells appear to play an important role in Th2-mediated allergic response and could be recruited through expression of CXCR3 and CCR6, as well as other chemoattractant receptors.

Th17

The role of Th17 cells in the allergic response is only beginning to be investigated. Recently, a murine model of asthma demonstrated that IL-17 is required for the induction of allergic asthma but negatively regulates established asthma (60). IL-17 production was increased following allergen challenge in this model and was further increased in the absence of regulation by the IL-4R α . Similar to the mouse model, human IL-17 was produced by peripheral blood T cells from allergic asthmatic subjects in response to allergic stimulus and was increased in the human asthmatic airway as compared to healthy controls (88–90). These data, along with observed patterns of chemoattractant receptor expression, suggest that Th17 cells are recruited to the asthmatic airway following allergen challenge through CCR4 and/or CCR6 and may be involved in both the initiation and regulation of the asthmatic response.

Treg

Recruitment of Tregs may play a role in the suppression of allergic inflammation. Depletion of CD4⁺ CD25^{hi} Tregs before sensitization with allergen led to an increase in Th2 cytokines, IgE concentrations, eosinophilia, and AHR in C3H mice normally resistant to the allergic asthmatic response (61). Adoptive transfer of antigen-specific Tregs into allergen-sensitized mice before allergen challenge inhibited AHR, eosinophil recruitment, and Th2 cytokine production through an IL-10-dependent process (63). These studies support the notion that Tregs play a key role in regulating the allergic asthmatic process.

The balance of Tregs likely regulates the allergic asthmatic response in humans, although this is still being investigated. A recent study showed that the frequency of allergen-specific IL-10-producing peripheral blood T cells was increased in healthy controls, whereas the frequency of allergen-specific IL-4-producing peripheral blood T cells was increased in atopic asthmatics (91). Because Tregs utilize IL-10 in regulation of T cell inflammatory processes, this study suggests that allergic asthmatics may lack high enough levels of IL-10 and thus Treg activity. In addition, a recent study has demonstrated that pediatric asthmatic subjects have a lower percentage of CD4⁺ CD25^{hi} BAL T cells than do children with chronic cough, healthy controls, or even asthmatic subjects treated with corticosteroids (92). Tregs may play a significant role in allergic asthma responsiveness following encounter with antigen.

The chemokine receptors expressed on Tregs, including CCR4, CCR5, CCR7, and CCR8, allow these cells to be recruited to either the allergic lung or lymph node to exert their regulatory activity following allergen challenge. Tregs appear to play an important role in regulating the allergic asthmatic response, but further study is required to understand the mechanisms by which they exert their activity and their requirements for tissue localization in this process.

CD1d-Restricted NKT Cells

A recent report has suggested that CD1d-restricted natural killer T (NKT) cells comprise the majority (>60%) of T cells in the asthmatic BAL as compared to healthy controls or subjects with sarcoidosis (64). However, although CD1d-restricted NKT cells were significantly enriched in the BAL as compared to blood, we have found that they made up only <2.5% of the lymphocyte gate (93). We believe that the discrepancy between the study by Akbari et al. (64) and our data (93) may be due to nonspecific staining from alveolar macrophages and cellular debris in the BAL. Further, following segmental allergen challenge, the percentage of BAL CD1d-restricted NKT cells was unchanged from prechallenge levels (22). This suggests that while CD1d-restricted NKT cells are enriched tenfold in the BAL as compared to peripheral blood, CD1d-restricted NKT cells are not the predominant T cell in the asthmatic BAL before or after segmental allergen challenge. Because CD1d-restricted NKT cells express high levels of CXCR3, CCR5, and CCR6 as well as intermediate levels of CCR4 (94), these receptors would be predicted to recruit CD1d-restricted NKT cells to the asthmatic lung but not with >1000-fold enrichment compared to peripheral blood NKT concentrations, as suggested by Akbari et al. (64).

More recent data are consistent with the conclusion that the frequency of CD1d-restricted NKT cells in the BAL may have been substantially overestimated, possibly for technical reasons (95). A number of other groups have also observed low numbers of BAL NKT cells in persons with mild, moderate, and severe asthma, subjects with chronic obstructive pulmonary disease (COPD), and healthy controls (95–99), in contrast to the findings of Akbari et al. (64).

In mouse models of asthma, CD1d-restricted NKT cells have also been shown to be critical for generating the allergic airway response through production of IL-4 and

IL-13 (65, 100). However, the requirement for CD1d-restricted NKT cells (and CD8 T cells) in the development of T cell-dependent airway inflammation has been called into question by a recent study that shows that CD4⁺ T cells, but not CD1d-restricted NKT or CD8 T cells, are sufficient to induce allergic airway inflammation (68).

Thus, although CD1d-restricted NKT cells likely contribute to the asthmatic response through secretion of Th2 cytokines, we believe that conventional T cells make up the predominant T cell population in the asthmatic BAL and play the predominant role in promoting the allergic asthmatic response.

CHEMOKINES AND CHEMOATTRACTANT RECEPTORS IN THE ALLERGIC ASTHMATIC RESPONSE

Although the recruitment of eosinophils into the airways is an important component in the pathogenesis of asthma (see the sidebar, Eosinophil Recruitment into the Lung During Allergic Inflammation), the trafficking of activated T lymphocytes into the airways clearly orchestrates the asthmatic inflammatory response (101). Consistent with this, after exposure to allergen, there is a dramatic increase in the number of T cells in the airways of humans and in murine models of asthma (1, 21, 22, 41, 71, 102, 103). In a murine model of asthma, we determined that the trafficking of Th2 cells into the airway both before and following allergen challenge is controlled by G protein-coupled chemoattractant receptors (104). Although CCR4 and CCR8 are expressed on Th2 cells, deletion of these receptors in mouse models of asthma has yielded conflicting results (105–110). The preservation of Th2 cell trafficking in the absence of individual chemoattractants or their receptors has led us to hypothesize that multiple pathways, acting through multiple chemoattractants and their receptors, direct Th2 cell trafficking into the airways.

Comparisons between normal controls and human asthmatics, as well as human segmental allergen challenge studies, have yielded information about T cell trafficking and chemoattractant receptor expression. At baseline, healthy controls and asthmatic subjects express similar chemokine receptors on BAL T cells (31, 84, 86, 111, 112). BAL T cells were enriched in expression of specific receptors as compared to peripheral blood T cells and expressed high levels of CCR5, CXCR3, and CXCR4; intermediate levels of CCR4, CCR6, CCR7, and CXCR6; and low levels of BLT1, CCR1, CCR2, CCR3, and CXCR1 along with other chemoattractant receptors. The increased expression of specific chemoattractant receptors on BAL T cells as compared to peripheral blood T cells may be related to the larger memory T cell population in the BAL and to the requirement for specific chemokine receptors in trafficking to tissue sites.

Following allergic stimulus, a number of chemokines are produced and lead to recruitment of T cells along with other leukocytes to the allergic lung. Human CCR2, CCR3, CCR4, CCR5, CCR6, CXCR1/2, CXCR3, CRTH2, but not CCR8 or CXCR6 ligands were increased following segmental allergen challenge (22, 102, 113–118). Similarly, in the mouse models of asthma, ligands of the chemoattractant receptors, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CXCR1, CXCR3, and BLT1 were induced in the lung at early time points (119–122). These data suggest that a number of chemokine receptors play a role in recruitment of T cells and other allergic mediators.

We and others have examined the profiles of chemoattractant receptor expression on T cells before and after segmental allergen challenge to determine whether specific chemoattractant receptors were preferentially utilized in T cell recruitment (22, 31). We hypothesized that the Th2-associated receptors CCR3, CCR4, and CCR8 would be increased following allergen challenge, whereas the Th1-associated receptors CCR5,

EOSINOPHIL RECRUITMENT INTO THE LUNG DURING ALLERGIC INFLAMMATION

Although T cells likely orchestrate allergic asthmatic inflammation, it is the eosinophil that remains the primary leukocyte recruited into the airway during allergic inflammation. Recent data indicate that eosinophils are necessary for the full manifestations of the asthma phenotype (17, 18), and thus the mechanisms that control their recruitment into the airway are important for asthma pathogenesis. Eosinophils express the chemokine receptor CCR3 and are likely recruited via production of the STAT6-dependent chemokines CCL11 and CCL24 (in both mice and humans) and CCL26 (in humans only), all of which are upregulated in the airways of asthmatics (117, 173–175). Data in animal models indicate that both CCL11 and CCL24 contribute to eosinophil recruitment, with CCL24 likely being the dominant eosinophil-active chemokine (176). STAT6 expression in a lung cell is necessary for eosinophil recruitment (41), and recent data (159) suggest that alternatively activated macrophages may mediate eosinophil recruitment. We also have data suggesting that myeloid DCs can express CCL24 and may also help mediate eosinophil recruitment (unpublished observation). These data demonstrate that eosinophil recruitment into the airway in allergic inflammation is largely controlled by myeloid cells in the lung via a STAT6-dependent mechanism.

CXCR3, and CXCR6 would be decreased following challenge. Although total numbers of T cells were increased following allergen challenge, we did not observe an increase in the percentage of CD4⁺ or CD8⁺ T cells expressing any chemoattractant receptor (22). Instead, we noted a statistically significant decrease in CCR6 and CXCR3 expression on CD4⁺ and CD8⁺ BAL T cells 24 h following allergen challenge. We believe that CCR6 and CXCR3 were downregulated following encounter with cognate ligand, indicating that these two receptors might play an underappreciated role in T cell recruitment to the asthmatic airway. However, we would also argue that these data have not ruled out the significance of other chemoattractant receptors in the recruitment of T cells to the allergic lung.

PAMP:

pathogen-associated
molecular pattern

Overall, these data suggest that T cells are recruited to the asthmatic BAL through a number of different chemoattractant receptors. Because the chemokines expressed following the asthmatic response can recruit a variety of T cells, it is important to understand the role of different T cell subsets in the asthmatic response.

THE PHASES OF T CELL TRAFFICKING IN ALLERGIC ASTHMA: A NEW PARADIGM

In the past few years, we and others have made considerable progress in delineating the mechanisms that control T cell trafficking in asthma. These data have led us to the central hypothesis of this review: T cell trafficking into the allergic lung is controlled by several discrete regulatory pathways that involve the collaboration of innate and acquired immune cells. We propose a four-step model that includes an initiation phase, a propagation phase, an amplification phase, and a resolution phase (**Figure 5**). The first two phases of T cell recruitment into the airways are mediated by chemoattractants produced by innate immune cells stimulated by the direct interactions of inhaled allergens. Binding and cross-linking of mast cell-associated IgE by allergens lead to mast cell activation, resulting in the release of a first set of chemoattractants that initiate T cell recruitment (phase I). We propose that early T cell recruitment is then propagated by the recognition of allergen by PAMP (pathogen-associated molecular pattern) receptors on innate immune cells in the lung, which leads to the release of chemokines (phase II). The third phase of T cell recruitment is mediated by chemoattractants produced in response to the interactions of resident airway cells with the Th2 cells arriving in the initiation and propagation phases of recruitment. These early recruited Th2 cells elaborate Th2-type cytokines that stimulate resident innate immune cells of the airways to release this third set of STAT6-inducible chemoattractants that dramatically

amplify Th2 cell recruitment (phase III), and also mediate eosinophil recruitment. Finally, a subset of T cells leaves the airways and enters the lymphatics during a resolution phase (phase IV) that we believe may be involved in both attenuating allergic pulmonary inflammation and in establishing immunologic memory. In this review, we present data that support this paradigm for the control of T cell migration into and out of the lung.

PHASE I: INITIATION—MAST CELL-DEPENDENT TH2 CELL RECRUITMENT

Within minutes of inhaling allergen, IgE on mast cells binds the foreign substance, leading to cross-linking of mast cell IgE Fc receptors (**Figure 5a**). This cross-linking stimulates the mast cells to release preformed inflammatory mediators, such as histamine, and also stimulates the cells to produce and release other mediators, including leukotrienes, TNF- α , chemokines, and Th2-type cytokines. These mediators start the development of mucosal edema, mucus secretion, and airway reactivity. In addition, some of these mediators initiate the recruitment of T cells into the airways (123, 124). We have recently shown that one of these mediators, LTB₄, is a potent chemoattractant for Th2 and Th1 cells (125–127). Furthermore, we have demonstrated that deletion of the LTB₄ receptor, BLT1, leads to an early defect in T cell accumulation in the airways in a model of allergic pulmonary inflammation that involves active immunization to a foreign antigen (chicken egg albumin or OVA) with IgE formation. However, this defect was not seen when OVA-specific Th2 cells were adoptively transferred into unimmunized mice, which do not form OVA-specific IgE (127). Because one of the important differences between these two models is the formation of IgE and mast cell stimulation with OVA challenge, these results led us to hypothesize that in response to allergen challenge, IgE-activated mast cells release LTB₄ into the airway, which mediates the

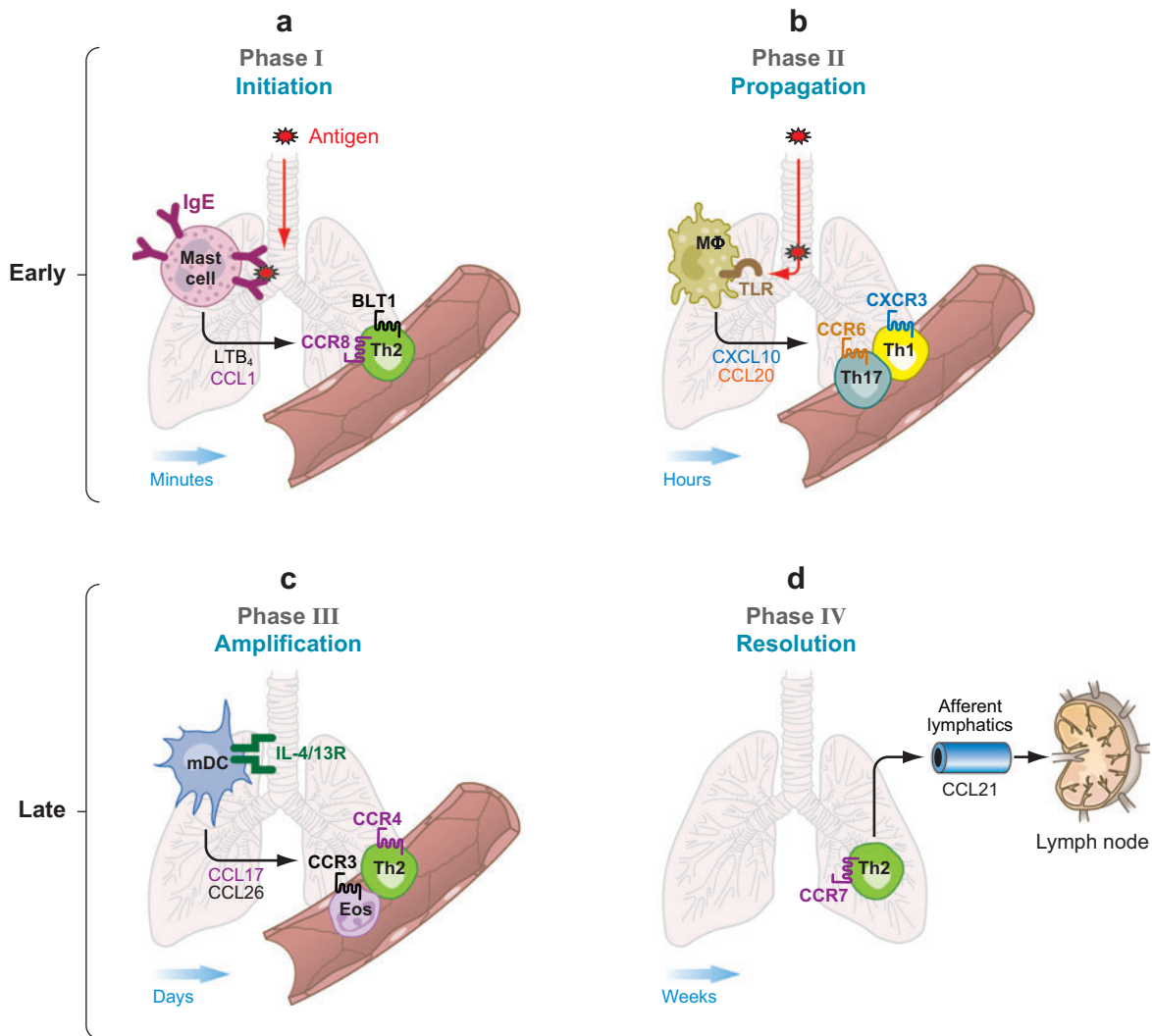


Figure 5

Proposed multiphase model of T cell trafficking into the asthmatic airway. (a) Phase I: initial T cell recruitment into the airways. Antigen-IgE complexes stimulate airway mast cells to release various mediators, such as leukotriene B₄ (LTB₄) and CCL1, which leads to Th2 cell recruitment through BLT1 and CCR8. (b) Phase II: propagation of T cell recruitment into the airways. Antigen directly interacts with innate immune cells, such as macrophages via TLRs, to stimulate the release of chemokines, such as CXCL10 and CCL20. These chemokines then recruit more T cells into the airways via their receptors CXCR3 and CCR6. (c) Phase III: proposed mechanism for amplification of T cell recruitment into the airways. IL-4 and IL-13 produced by Th2 cells already recruited into the airways stimulate innate immune cells, such as myeloid DCs, to release the STAT6-dependent chemokines CCL17 and CCL22. These chemokines amplify Th2 cell recruitment into the airways through their receptor CCR4. (d) Phase IV: proposed mechanism for resolution of T cell accumulation in the airways. Th2 cells in the airways that express CCR7 are recruited into the lymphatics through the action of CCL21. This then leads to efflux of the Th2 cells out of the lung and into the lymph node.

TLR: Toll-like receptor

initial recruitment of Th2 cells into the lung (126).

Mast cells also produce and release the chemokines CCL1, CCL17, CCL22, and the chemical histamine, all of which are chemotactic for Th2 cells through interactions with their G protein-coupled receptors CCR8 (CCL1), CCR4 (CCL17, CCL22), and H1R (histamine) (123, 128–130). CCL1 release may be particularly important for early Th2 cell recruitment, as recently demonstrated in a murine model of mast cell-dependent allergic airway inflammation (130). Mast cell stimulation by allergen-IgE complexes thus leads to the release of multiple chemoattractants able to initiate the recruitment of T lymphocytes into the airways. The sequential release of LTB₄ and chemokines from mast cells is consistent with the differing time courses of the generation of these chemoattractants: LTB₄ is rapidly generated enzymatically from membrane lipids within minutes, whereas the release of chemokines may require transcription and translation and consequently take several hours. In addition to generating leukotrienes, activated mast cells also generate prostaglandins, including PGD₂, which could lead to Th2 cell recruitment through the CRTH2 receptor (131–133).

In addition to preformed IgE antibodies, IgG antibodies to allergens can also stimulate mast cells and macrophages to release inflammatory mediators (134–136). These mediators, which include LTB₄, can further enhance the recruitment of T cells into the airways following allergen exposure.

The initial recruitment of T cells in the airways allows the immune system to respond to a perceived threat within minutes as opposed to the hours it would take to mount an adaptive immune response. DC maturation and function may also depend on an initial interaction with memory T cells in the airways (8). Thus, the almost immediate recruitment of memory T cells into the airways following allergen challenge may also help prime the adaptive immune response by increasing potential DC–T cell interactions. Furthermore,

mast cell degranulation may contribute to the efficiency and intensity of the LAR by enhancing T cell recruitment into the airways (124, 127).

In summary, soon after the inhalation of allergen, antigen interaction with preformed IgE and IgG antibodies leads to early mediator release, including chemoattractants. These chemoattractants then rapidly induce the initial recruitment of T cells into the airways.

PHASE II: PROPAGATION—INNATE IMMUNE-DEPENDENT TH2 CELL RECRUITMENT

In addition to binding to antigen-specific antibodies, components in allergens, or associated viral infections or particles in the air, can stimulate innate immune cells in the airways through interactions with PAMP receptors, such as the TLRs (**Figure 5b**). TLR stimulation in asthma exacerbations may occur through LPS (lipopolysaccharide) found in antigens. In addition, viral infections (a common cause of asthma exacerbations) can stimulate innate immune cells as well as epithelial cells via TLR stimulation (137–140). We have previously shown that most Th2 cell recruitment into the lung following allergen challenge is dependent on tissue-derived STAT6-induced chemokines, such as CCL22 and CCL17. Although STAT6 plays a significant role in the regulation of antigen-specific Th2 cell trafficking, there is evidence that STAT6-independent pathways contribute to T cell trafficking into the allergic lung. Namely, after the adoptive transfer of antigen-specific Th2 cells and antigen challenge, a small number of antigen-specific Th2 cells do enter the lung of STAT6^{-/-} mice (41, 104). We hypothesize that PAMP receptor-inducible chemokines and their corresponding chemokine receptors represent a STAT6-independent pathway of antigen-specific Th2 cell and Th1 cell trafficking. This could have direct relevance to upper respiratory viral

infections, such as the influenza virus (141) or respiratory syncytial virus (142), which can activate TLR7 and TLR3. In addition, aeroallergens, like animal dander and house dust mites, contain LPS.

The importance of TLRs in asthma is indicated by studies demonstrating that the inflammatory response in a murine model of asthma is partially dependent on the adaptor molecule, MyD88, a downstream mediator of TLR signaling (12). In addition, LPS in allergens can stimulate antigen-presenting cells in the lung and may play role in Th2 cell polarization (143). Recently, Jung et al. (144) have shown that TLR4 stimulation in an animal model of allergic airway inflammation enhances both Th1 and Th2 cell recruitment into the lung. Consistent with this, there is evidence in the published literature that TLR activation leads to CXCL10 and CCL20 expression (145, 146) and that CXCL10 and CCL20 are increased in the context of allergen exposure (22, 102, 121, 122, 147, 148). CXCR3 and CCR6, the receptors recognizing CXCL10 and CCL20, are expressed on T cells that infiltrate the lung during allergic inflammation (22, 31, 111). Furthermore, CCR6-deficient mice have decreased airway resistance, fewer lung eosinophils, and reduced lung IL-5 levels compared with their wild-type counterparts (121, 149), and the transfer of CCR6^{+/+} T cells from sensitized wild-type mice into CCR6^{-/-} mice results in an increase in airway eosinophilia and IL-5 levels (149). In addition, studies with the CXCL10 knockout and transgenic mice suggest that recruitment of CXCR3⁺ T cells exacerbates the allergic asthmatic response (122). These data are also consistent with some of our recent findings suggesting that CXCR3 and CCR6 are mediators of T cell recruitment into the airways of asthmatics following allergen challenge (22).

Although Th2 and Th1 cells are likely the primary mediators of allergic airway inflammation, some data suggest that other T cell subsets may also be involved in asthma pathogenesis. These include Th17 cells, NKT cells,

CD8⁺ T cells, and $\gamma\delta$ T cells. Th17 cells express CCR6, for which the ligand (CCL20) is made in this phase (44, 150, 151). In addition, NKT cells, CD8⁺ T cells, and $\gamma\delta$ T cells may all be recruited by similar mechanisms as Th1 cells in this phase, with CXCL10 and CCL20 both potentially mediating the recruitment of these cells (22, 94, 152).

Allergen deposition in the lung may also interact with other inflammatory pathways, such as the complement cascade, and enzymes in the airways, such as chitinases, which could then influence the production of chemokines (153, 154). For example, the activation of the C5a receptor following allergen challenge increases the secretion of the CCL17 and CCL22 by airway DCs in a murine model of asthma.

These data suggest that allergen-induced pattern recognition receptor stimulation on innate immune cells in the lung may contribute to T cell recruitment. We hypothesize that allergen or viral components directly stimulate innate immune cells, activating these cells to present antigen and to produce chemokines and other inflammatory cytokines. These mediators then propagate the inflammatory response and enhance the recruitment of Th2 cells into the lung. In addition, these mediators may also initiate the recruitment of Th1 cells and other T cell subsets into the lung, which could further enhance the homing of Th2 cells into the lung (58, 59, 144).

PHASE III: AMPLIFICATION— STAT6-DEPENDENT TH2 CELL RECRUITMENT

Following the early trafficking of Th2 cells into the airways, there is a dramatic amplification of Th2 cell recruitment (**Figure 5c**). Previous research by our group has shown that deletion of STAT6 in the lung eliminates more than 80% of Th2 cell trafficking following allergen (41, 42). These studies also demonstrated that STAT6 expression in a resident lung cell is necessary for effective

Th2 cell and eosinophil recruitment into the airways. Consistent with this finding, STAT6^{-/-} mice had significantly lower production of the Th2-active chemokines CCL17 and CCL22 and the eosinophil-active chemokines CCL11 and CCL24. Using a model of pulmonary Th2 inflammation induced by infection by *Nippostrongylus brasiliensis*, Voehringer et al. (19, 20) demonstrated that STAT6 expression in a bone marrow-derived myeloid cell is necessary for Th2 cell trafficking into the lung. These data suggest that the critical cellular mediator of Th2 cell recruitment is a bone marrow-derived nonlymphocyte cell in the lung, possibly a myeloid-derived cell such as a pulmonary macrophage or DC. We hypothesize that Th2 cells recruited into the lung in the initial and propagation phases produce IL-4 and IL-13 (155), which stimulate myeloid-derived cells in the lung, such as pulmonary macrophages and/or DCs, to produce STAT6-dependent chemokines. These chemokines then serve to amplify the recruitment of Th2 cells and initiate eosinophil trafficking into the lung.

Previous work by others has demonstrated that depletion of CD11c⁺ cells in the lung after sensitization to OVA but prior to challenge prevents the development of allergic airway inflammation, suggesting that airway DCs and/or alveolar macrophages (both are CD11c⁺) control key aspects in the pathogenesis of the inflammatory response (156). When alveolar macrophages or DCs were added back to the lung in those experiments, the phenotype was restored only with DC transfer, suggesting that DCs were necessary for allergic inflammation. In addition, pulmonary DCs accumulate around the airways during allergic inflammation and produce CCL17 and CCL22 (9, 153, 156, 157, 158). We have recently found that selective depletion of a population of CD11b⁺/CD11c⁺ myeloid DCs in the lung significantly impairs Th2 cell trafficking into the lung following Th2 cell transfer and antigen challenge (B.D. Medoff and A.D. Luster, unpublished observation). Our data demonstrate that myeloid

DCs in the lung are both necessary and sufficient for Th2 cell trafficking in this model. Based on these data, we propose that Th2 cells recruited into the airways in the initiation and propagation phase produce cytokines that stimulate pulmonary myeloid DCs to make CCL17 and CCL22, which amplifies Th2 cell recruitment into the airways. In addition, these cells, as well as alternatively activated pulmonary macrophages (159), produce CCL24, which stimulates eosinophil recruitment into the airways.

Tregs likely are involved in the control of airway inflammation and have been shown to accumulate in the airway during the development of allergic inflammation in an animal model of asthma (62). Tregs express the chemokine receptors CCR4 and CCR8 (56) and thus may be recruited by the release of CCL1 during phase I, and CCL17 and CCL22 during phase III of the paradigm.

PHASE IV: RESOLUTION/ MEMORY—CCR7-DEPENDENT TH2 CELL EXIT

In murine models of asthma, intense airway inflammation produced by sensitization and challenge with allergen decreases over time following the cessation of allergen exposure (160–162) (**Figure 5d**). The resolution of airway inflammation following allergen challenge is clearly an important process for limiting the allergic response and may prevent complications of inflammation. For example, deletion of matrix metalloproteinase-2 expression in a murine model of asthma reduced the efflux of inflammatory cells out of the lung, which slowed the resolution of airway inflammation and was associated with increased mortality from asphyxiation (163). Despite its potential importance in asthma, the mechanisms of Th2 cell clearance from the lung are poorly understood. Some cells may become apoptotic (160), and others are likely cleared with expectoration (163). Recently, we have demonstrated that a subset of Th2 effector cells express CCR7 and migrate

into the lymphatics under the guidance of CCL21 expression (33). Although the exact contribution of this CCR7-directed migration for Th2 cell egress from the lung remains to be determined, this may be one of several mechanisms involved in the resolution of allergic airway inflammation. In addition, migration of Th2 cells from the lung into the lymphatics may help establish immunologic memory and, importantly, contribute to future exacerbations following allergen reexposure. We propose that CCR7-mediated T cell egress from the asthmatic lung contributes to both the resolution of a primary allergic response as well as to the establishment of T cell memory and generation of local lung recall immune responses.

EXPANSION OF THE PARADIGM FOR OTHER LUNG CELL TYPES

The contributions of structural lung cells, such as epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells, in asthma pathogenesis remain less well defined than other innate immune cells in the lung. All these cell types produce chemokines when properly stimulated (164–173) and thus may

also contribute to T cell recruitment into the lung in asthma. However, our data and data from others indicate that mast cells and myeloid cells in the lung are likely the primary mediators of T cell recruitment (19, 20, 156)

CONCLUSIONS

In this review, we have tried to identify the critical mediators of T cell migration into and out of the lung during the development and resolution of allergic airway inflammation. On the basis these data, we propose a new paradigm in T cell trafficking in asthma, involving three phases of chemoattractant-directed T cell recruitment into the lung, followed by a resolution phase of chemoattractant-directed T cell exit (**Figure 5**). This paradigm involves extensive interactions between the innate immune cells in the lung and T cells. In addition, each phase is regulated by distinct mechanisms, providing an overlapping network of pathways involved in T cell recruitment. This new paradigm may help provide novel insights into the pathogenesis of asthma and identify potential therapeutic targets to treat this common disorder.

SUMMARY POINTS

1. Asthma is a chronic inflammatory disease of the airways that is often caused by an allergic-type reaction to antigen.
2. In most cases the inflammatory reaction is orchestrated by CD4⁺ T cells that are recruited into the airways.
3. Recruitment of T cells into the lung is orchestrated by secretion of chemokines and chemoattractants in response to allergen exposure.
4. IgE-stimulated mast cells mediate early T cell recruitment through the secretion of leukotriene B₄ and the chemokines CCL1, CCL17, and CCL22.
5. Allergen may also directly stimulate early T cell recruitment into the airway through interaction with PAMP receptors on macrophages, leading to secretion of chemokines, such as CXCL10 and CCL20.
6. The great majority of T cell recruitment is mediated by exposure of mucosal DCs to the cytokines IL-4 and IL-13, which leads to STAT6-mediated secretion of CCL17 and CCL22.

7. Tregs may also be recruited into the airways via the action of chemokines.
8. Some T cells in the airways express CCR7 and are recruited out of the lung back into lymphoid tissue, which may reduce airway inflammation but may also provide a mechanism for memory responses to allergens.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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19 and 20. These two papers demonstrated that bone marrow-derived myeloid cells control Th2 cell recruitment into the lung during the establishment of a type 2 immune response.

22. Found that multiple chemokine receptors are expressed on T cells recruited into the airway of allergic asthmatic individuals following allergen challenge, including chemokine receptors associated with Th1 cells.

23. Demonstrated that adoptively transferred Th2 cell effectors migrated into the lymph node and lung parenchyma. Following allergen challenge, lymph node T cells proliferated and migrated into lung tissue; T cells in the lung did not proliferate but produced cytokines.

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