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T cell homing to epithelial barriers in allergic disease

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Abstract

Allergic inflammation develops in tissues that have large epithelial surface areas that are exposed to the environment, such as the lung, skin and gut. In the steady state, antigen-experienced memory T cells patrol these peripheral tissues to facilitate swift immune responses against invading pathogens. In at least two allergy-prone organs, the skin and the gut, memory T cells are programmed during the initial antigen priming to express trafficking receptors that enable them to preferentially home to these organs. In this review we propose that tissue-specific memory and inflammation-specific T cell trafficking facilitates the development of allergic disease in these organs. We thus review recent advances in our understanding of tissue-specific T cell trafficking and how regulation of T cell trafficking by the chemokine system contributes to allergic inflammation in mouse models and in human allergic diseases of the skin, lung and gut. Inflammation- and tissue-specific T lymphocyte trafficking pathways are currently being targeted as new treatments for non-allergic inflammatory diseases and may yield effective new therapeutics for allergic diseases.

Sensitization to allergens and epithelial-barrier dysfunction

Atopic sensitization commonly occurs early in life if epithelial barrier integrity is compromised and the epithelium becomes aberrantly activated, which may occur through a complex interplay of environmental insults and host factors¹. For example, filaggrin loss-of-function mutations that compromise epithelial barrier integrity have been associated with an increased risk for developing eczema and asthma^{1,2}. Barrier dysfunction in the lung and skin allows allergens to activate the epithelium and produce cytokines that are permissive for the induction and development of T helper type 2 (T_H2) responses, such as interleukin-33 (IL-33), thymic stromal lymphopoietin (TSLP) and IL-25 (Fig. 1)^{1–10}. A dysfunctional epithelial barrier also allows antigen-sampling dendritic cells to become directly activated by allergens and undergo maturation in a T_H2-permissive milieu such that they subsequently prime allergen-specific T_H2 responses^{1,6,8}.

Programmed T cell trafficking and allergic disease

Accurate and efficient tissue-specific trafficking between the circulation, lymphoid organs and peripheral tissues is a fundamental prerequisite for effector T cell function and results in either host immunity or tissue immunopathology. Leukocytes coordinately use adhesion molecules in a highly regulated process to directionally extravasate from the blood into target peripheral tissues¹¹. These adhesion molecules include selectins, integrins and chemoattractant receptors. Selectins are a conserved family of C-type lectins and include L-

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selectin and P-selectin glycoprotein ligand 1 (PSGL1) and promote the rolling movement of leukocytes along the surfaces of endothelial cells¹¹. Integrins are a family of two-chain type I transmembrane receptors and include leukocyte function-associated antigen 1 LFA-1 (CD11a–CD18 or $\alpha_L\beta_2$) and $\alpha_4\beta_7$ and are involved in the firm adhesion of leukocytes to endothelial cells¹¹. Chemoattractant receptors are a family of G protein–coupled receptors (GPCRs) that activate integrins through inside-out signaling to initiate firm adhesion and induce directed cell migration through tissue gradients of their ligands and include chemokine and lipid chemoattractant receptors¹¹. During inflammation, ligands for selectins, integrins and chemoattractant receptors are upregulated in tissue and vascular beds and provide directional cues for inflammatory T cells, on which the corresponding receptors are upregulated, to enter inflamed tissue from the blood. In addition to inflammation-regulated trafficking cues, allergy-prone organs such as the skin and the small intestine provide an additional level of specificity in T cell trafficking to these organs through a process known as ‘imprinting’^{11–13}.

The profile of integrins, selectins and chemokine receptors expressed by T cells is determined by their states of activation, polarization and differentiation, as well as their initial tissue site of antigen priming, leading to tissue-specific imprinting in some organs^{13–16}. Tissue-specific imprinting is best characterized in the small intestine and the skin, as preferential homing to these organs was discerned more than two decades ago^{17–21}. Naive, effector and memory T cells have distinct trafficking patterns within the circulation, lymphoid organs and peripheral tissue (Fig. 1). After T cell receptor activation, naive T cells differentiate into effector T cells (Fig. 1), which express an altered profile of trafficking receptors; some of these trafficking receptors are maintained in steady-state memory T cells after inflammation is resolved^{14,15}. During the initial priming of naïve T cells, some allergy-prone organs that are exposed to the environment ‘program’, or imprint, preferential tissue-specific inflammatory effector T cell and memory T cell entry from the circulation to streamline immune surveillance, as many microbes are tissue tropic in virulence^{12,17,22}.

T cells that are programmed to home to the small intestine are imprinted during the initial antigen priming to specifically express integrin $\alpha_4\beta_7$ and the chemokine receptor chemokine (C-C motif) receptor 9 (CCR9), expression of which enables restricted and regulated entry into the small intestine^{23,24} (Fig. 2). In contrast, the signature-homing receptors of skin-tropic T cells are the lectin cutaneous leukocyte antigen (CLA), which is derived from the glycosylation of PSGL1, in combination with the chemokine receptors CCR4 and CCR10 and, for some T cell subsets, CCR8 and CCR6 (Fig. 2)^{20,25–32}. Low levels of the ligands for these receptors are constitutively expressed in the steady state to facilitate tissue-specific memory T cell homing and immune surveillance^{30,33–36}. Higher levels of the ligands induced during inflammation promote increased tissue-specific effector T cell homing. Notably, mechanisms that facilitate gut- and skin-specific imprinting are dependent on tissue-specific dendritic cells and tissue-specific environmental cues^{12,22}. In the gut, CD103⁺ ($\alpha_E\beta_7$ integrin) lamina propria and Peyer’s patch dendritic cells produce high concentrations of retinoic acid; retinoic acid enables these dendritic cells to imprint expression of the gut-tropic receptors $\alpha_4\beta_7$ and CCR9 on naive T cells^{37–42}. Likewise, skin dendritic cells can generate high concentrations of the active vitamin D3 metabolite, 1,25(OH)₂D3, and then use it to induce CCR10 expression on T cells in higher mammals^{22,43}.

Studies suggest that the lungs and nasal-associated lymphoid tissue (NALT) also program T cells for tissue-specific homing^{12,44}. High endothelial venules in NALT express high amounts of peripheral node addressin (PNAd), the ligand for CD62L, the expression of which distinguishes NALT from other mucosal-associated tissues, such as Peyer’s patches. Programmed allergen-specific T cell entry into NALT through interactions with PNAd

promotes allergic rhinitis⁴⁴. Though not definitive, lung-specific imprinting is suggested by human studies in which CD8⁺ T cells specific for respiratory, but not systemic, viruses were selectively enriched in human lungs, analogous to the enrichment of CLA^{hi} T cells specific for skin-tropic but not systemic viruses in the skin^{45,46}. Steady-state human lung-resident T cells are also reported to be enriched for CCR5, CCR6, chemokine (C-X-C motif) receptor 3 (CXCR3) and the integrins VLA1 ($\alpha_1\beta_1$), α_E ($\alpha_E\beta_7$ or CD103) and VLA4 ($\alpha_4\beta_1$)^{47–49}. However, the cellular mechanisms and environmental cues that promote lung-specific T cell imprinting have not been elucidated.

A consequence of naive T cell priming at any tissue site is the generation of memory T cells after the resolution of inflammation; recently a category of memory T cells known as tissue-resident memory T cells (T_{RM}) has been characterized⁵⁰ (Fig. 1). Based on functional traits that are linked to the ability to traffic to either secondary lymphoid tissue or peripheral tissue, memory T cells are classified into ‘central memory’ and ‘peripheral memory’ T cells⁵¹ (Fig. 1). Central memory T cells preferentially traffic between secondary lymphoid tissue and the systemic circulation, whereas effector memory T cells preferentially home to peripheral tissue from the blood^{14,15,51} (Fig. 1). A fraction of antigen-primed effector T cells differentiate into long-lived antigen-specific memory T cells, some of which persist throughout the lifetime of the host⁵⁰. Recent studies have suggested that large pools of tissue T_{RM} cells with enhanced effector capabilities persist in uninflamed peripheral organs, such as the lung, skin and gut, and provide a first line of defense against pathogens (Fig. 1)^{32,48,50,52–58}.

In the context of allergic diseases, programmed homing pathways increase the likelihood that tissue-patrolling memory T cells will encounter activated dendritic cells that present a cognate allergen in the tissue as well as in the draining lymph nodes. Sensitization to environmental allergens at the epithelial surfaces will generate long-lived allergen-specific memory T cells that are programmed to home to the mucosal and epithelial surfaces for immune surveillance. Concordantly, allergen-induced pathological activation of the epithelial barrier, through the production of cytokines such as IL-33, TSLP and IL-25, enhances the activation and maturation of T_H2 -priming dendritic cells. Prior and recurrent allergen exposure will also generate higher frequencies of recirculating allergen-specific memory T cells, as well as long-lived allergen-specific T_{RM} cells at the tissue sites of allergen exposure (Fig. 1). Thus, instead of being a very rare event, programmed homing pathways increase the likelihood that after allergen re-exposure, tissue-patrolling recirculating memory T cells and T_{RM} cells encounter cognate allergen presented by dendritic cells, particularly if the epithelial barrier is compromised⁵⁹.

Programmed regulatory T cell trafficking to the epithelial barrier

Programmed trafficking pathways that promote T cell-mediated allergic inflammation are also used by regulatory T (T_{reg}) cells to rein in inappropriate responses at mucosal and epithelial surfaces. The dendritic-cell-derived factors retinoic acid and 1,25(OH)₂D3 can be either proinflammatory or anti-inflammatory^{60–65}. In the intestine, retinoic acid derived from CD103⁺ mucosal dendritic cells induces forkhead box P3 (Foxp3)⁺ T_{reg} cell differentiation from naive T cells after *in vivo* activation^{63,65,66}. Retinoic acid also imprints Foxp3⁺ adaptive T_{reg} cells in the mesenteric lymph node (MLN) to acquire expression of $\alpha_4\beta_7$ and CCR9 to enable homing to the small intestine from the MLN⁶¹. In mice deficient for integrin β_7 or the integrin ligand mucosal vascular addressin cell adhesion molecule 1 (MADCAM1), oral tolerance is abrogated, as T_{reg} cells fail to traffic from the MLN to the lamina propria⁶⁷. In contrast, in the presence of pro-inflammatory cytokines, such as IL-15, retinoic acid can act as an adjuvant to promote inflammatory responses to dietary antigen⁶⁸. In the skin, skin-tropic effector memory T cells and skin-tropic T_{reg} cells share receptor

profiles comprised of CCR4, CLA and CCR8, which suggests that common environmental cues may imprint proinflammatory and anti-inflammatory T cell homing pathways to the skin^{13,69}. T_{reg} cells exert their suppressive effects by localizing to lymphoid organs during the induction of the immune response and to peripheral tissues during the ongoing immune response^{13,67,70–72}. For example, oral tolerance to ingested soluble antigen is initiated during the inductive phase of the immune response in the MLN, and oral tolerance is abrogated after mesenteric lymphadenectomy and in CCR7-deficient mice⁷¹. An altered epithelial barrier may allow proinflammatory cytokines or persistent allergen exposure to tip a programmed tissue-tropic pathway that promotes tolerance to innocuous allergens toward one that induces allergic inflammation.

Tissue-resident memory T cells and allergic disease

A convincing body of work over the past decade has shown that antigen-experienced effector memory CD4 and CD8 T cells persist for long periods of time in uninflamed peripheral tissue as functional T_{RM} cells^{32,48,50,52–58}. Steady-state migration of pathogen-specific memory CD8 T cells from the circulation into the lung, skin and gut is more restricted compared to other peripheral organs^{55,56}. In infectious models, memory CD8 T cell persistence is antigen dependent in the lung and is antigen independent in the skin and intestine^{55,73}. Re-exposure to antigen can also increase the size of the T_{RM} cell pool⁵⁷. T_{RM} CD4 and CD8 T cells can be activated by antigen-presenting dendritic cells in tissue before activation by dendritic cells in the draining lymph nodes^{54,58,74}. In addition to a functional role for T_{RM} cells in host immunity to pathogens, a functional role for T_{RM} cells has been shown in chronic inflammatory disease^{53,75}. Memory CD4 T cells derived from human psoriasis skin and grafted into mouse dermis are sufficient for induction of disease in a xenotransplantation model of psoriasis⁷⁵.

In humans, large reservoirs of T_{RM} cells have been reported in the skin and lungs^{32,48}. Twice as many T_{RM} cells are present in healthy skin compared to blood, and 98% of all CLA⁺ T cells are found in the skin in the steady state³². Likewise, steady-state T_{RM} cells in the human lung are equivalent in number to the circulating steady-state memory T cells in the blood⁴⁸. Consistent with *in vivo* mouse studies, these lung T_{RM} cells are not anergic, and they produce effector cytokines after activation⁴⁸. Moreover, only lung T_{RM} cells robustly proliferated *ex vivo* in response to influenza virus, a respiratory pathogen, in an antigen-specific manner, whereas skin-resident and blood T cells did not⁴⁸.

It is unclear whether and how T_{RM} cells modulate allergic inflammation. The traditional thinking has been that the hugely expanded pool of allergen-specific effector T cells derived from dendritic-cell-activated central memory T cells express inflammatory chemokine receptors that enable their exit from lymphoid organs and their entry into peripheral sites of inflammation from the circulation⁷⁶. Although the majority of effector T cells in a recall response are probably derived from central memory T cells, this paradigm may require revision with the appreciation that pre-existing tissue pools of T_{RM} cells can be activated by tissue-resident dendritic cells. T_{RM} cells may locally modulate allergic responses during the initiation phase of an allergen-specific recall response within the first few days after exposure, before lymph-node-derived amplified allergen-specific effector T cell entry into inflamed tissue from the bloodstream.

Inflammatory T_H2 cell trafficking

CD4 T_H cells have a pivotal role in mediating adaptive immunity to diverse pathogens and in promoting autoimmune diseases and allergic inflammation⁷⁷. During inflammation and after T cell receptor (TCR) activation, specific cytokines derived from the innate immune

system and distinct master transcription factors program naive T_H cells to differentiate into T_H1, T_H2, T_H17, T_{reg} and follicular T helper (T_{FH}) cell subsets⁷⁷. The master transcriptional regulators T-box 21 (T-bet), GATA binding protein 3 (GATA3), RAR-related orphan receptor γ (ROR- γ T), FOXP3 and B cell CLL/lymphoma 6 (BCL6) drive T_H cell subset differentiation and impart specificity of T_H cell lineage function through the production of signature effector cytokines⁷⁷ (Fig. 3). Repeated antigen exposure and progressive lineage polarization also promote terminal T_H1 and T_H2 cell differentiation through epigenetic modifications at the *Ifng* and *Il4* loci to enable rapid effector cytokine production after antigen rechallenge⁷⁸. Polarizing cytokines and master transcription factors that promote T_H1, T_H2 and T_H17 cell lineage differentiation also program the expression of unique combinations of inflammation-specific chemokine receptors on T_H cell lineages during priming^{13,15,79} (Fig. 3). Thus, T_H2 cells are programmed during lineage differentiation to selectively express the chemokine receptors CCR4, CCR8 and, in humans, the prostaglandin D2 chemoattractant receptor DP2 or CRTH2 (refs. 79–81), which are associated with T_H2-type inflammation.

T_H2 cell heterogeneity

T_H2 cells can also be divided into an IL-4^{hi}IL-5^{lo} subset and a more differentiated IL-4^{lo}IL-5^{hi} subset, which can be distinguished by their expression of CCR4 or CCR8, respectively^{29,82}. Upregulation of CCR4 expression on T_H2 cells occurs rapidly after TCR ligation irrespective of prior antigen exposure and the extent of T_H2 differentiation^{29,83}. However, CCR8 expression and robust expression of IL-5 in T_H2 cells is restricted to more terminally differentiated T_H2 cells that have previously been exposed to antigen^{29,69,82,84,85}. Other examples of lineage-specific gene expression in more terminally differentiated T helper subsets include the IL-33 receptor (also called T1ST2 or ST2) in more terminally differentiated T_H2 cells and hepatitis A virus cellular receptor 2 (TIM3) in highly differentiated T_H1 cells^{86,87}.

Although it was previously believed that highly differentiated T helper subsets are fixed with regard to lineage differentiation, plasticity in T_H17, T_{reg}, T_{FH} and T_H2 cell lineage differentiation is now appreciated, as is the fact that additional T_H2 cell subsets exist *in vivo* during chronic inflammation^{88–90}. Virus infection and the induction of interferons reprogram antigen-specific, IL-4–producing GATA3⁺ T_H2 memory cells to become T_H2+1 cells that coexpress GATA3 and T-bet and secrete both IL-4 and interferon γ (IFN- γ)⁸⁸. Likewise, T_H2 memory cells differentiate into a subset of IL-17–producing T_H2 cells that coexpress GATA3 and ROR- γ T in severe chronic allergic inflammation that manifests a robust mixed neutrophilic and eosinophilic infiltrate *in vivo*⁸⁹.

This heterogeneity of T_H2 cells should be kept in mind, as the original studies that elucidated T_H cell subset biology were primarily conducted in tissue culture in the presence of neutralizing antibodies to generate pure T_H cell lineages. During chronic inflammation in the absence of neutralizing antibodies *in vivo* and in the setting of genetic and environmental heterogeneity, human allergic disease is more complex and involves the simultaneous production of multiple cytokines. This is concordant with the current appreciation that human asthma is a heterogeneous disease and that therapeutic strategies that target a single T_H2 cell cytokine may only be effective in subpopulations of patients with asthma in which the therapeutic intervention is matched to the underlying pathophysiology^{91,92}. Thus, *ex vivo* studies of human peripheral blood T cells have not provided a clear cut correlate of T_H1 and T_H2 effector cell cytokine production and the signature chemokine receptors that are associated with pure T_H1 and T_H2 lineage-differentiated cells^{16,93}. It therefore follows that T cell-mediated allergic disease probably involves multiple chemokines and their receptors,

the relative roles of which will vary depending on the affected organ and the temporal phase of the disease. We illustrate these points in the following sections.

T lymphocyte trafficking in atopic disease

Atopic dermatitis

The role of CD4⁺ T cell effector functions in the pathogenesis of atopic dermatitis has been established in both mouse and human studies^{94,95}. In human atopic dermatitis, a number of skin-homing trafficking receptors, such as CLA, CCR4, CCR10 and CCR8, as well as their ligands, have been implicated and reported to correlate with disease activity^{94,96–99}.

Although the contributions of CCL17 and CCL27 in the recruitment of human memory CD4 T cells from the blood to the sites of skin inflammation are well established, a correlation of skin CCL17 and CCL27 transcripts with specific inflammatory human disease phenotypes has not been found¹⁰⁰. In contrast, comparative analyses of all known chemokine RNA transcripts in healthy skin from control individuals and lesional skin from individuals with different chronic inflammatory skin disorders found significant and specific induction of the chemokines CCL1 and CCL18 in inflamed atopic dermatitis skin^{34,101}. Currently, the receptor for CCL18 is not known, although CCL18 binds skin-tropic CLA⁺ memory T cells in patients with atopic dermatitis and induces *in vivo* migration of human memory T cells¹⁰². Additionally, microarray analyses have revealed that expression of the enzyme fucosyltransferase VII (FucT-VII), which regulates CLA expression, as well as the chemokine receptors CCR4 and CCR10, was significantly elevated in blood CD4⁺ T cells from individuals with atopic dermatitis compared to healthy controls^{103,104}. Notably, the frequency of CLA⁺ blood T cells correlates with disease activity and skin inflammation in both contact hyper-sensitivity and atopic dermatitis¹⁰⁵. Additional studies have suggested a role for chemokine (C-X3-C) receptor 1 (CX3CR1) and its ligand, CX3CL1, in active atopic dermatitis and are concordant with studies that suggest a role for CX3CR1 in asthma^{106–108}.

The *in vivo* role of trafficking receptors that regulate T cell-mediated atopic skin inflammation has recently been clarified in two complementary studies that used a 7-week treatment schedule in a mouse model of chronic atopic dermatitis¹⁰⁹. CCL27 promotes atopic dermatitis in this model²⁸. Recent studies highlighted how the kinetics of chemokine and chemokine-receptor expression, tissue-specific T cell trafficking and tissue reservoirs of antigen-specific T cells might regulate cutaneous inflammation during acute, recurrent or chronic allergen exposure (Fig. 4)^{29,110}. CCR4 is essential for the acute entry of T cells into the skin through the cutaneous vasculature and drives atopic inflammation in antigen-naïve skin, in which pre-existing skin-resident reservoirs of antigen-specific memory T cells are absent¹¹⁰. Thus CCR4 is crucial for T cell entry into the skin during the initiation phase of cutaneous allergic inflammation, which is concordant with the rapid kinetics of the induction of its ligand, CCL17, in skin endothelium and with findings in other models of acute cutaneous inflammation^{25,111}. However, after repeated cutaneous allergen sensitization, CCR4 is not necessary for the entry of T_H2 cells from cutaneous vascular beds into the skin to sustain chronic eosinophilic atopic inflammation²⁹. In this setting, pre-existing skin pools of allergen-specific memory T_H2 cells are probably sufficient to initiate and drive local inflammatory responses through effector cytokine production after activation by skin-resident antigen-presenting cells. In contrast, in this setting, both CCR8 and its newly described second ligand, mCCL8 (a ligand for CCR8 in the mouse), are essential for promoting IL-5-driven eosinophilic inflammation in chronic atopic dermatitis²⁹. After 7 weeks of treatment, when peak atopic inflammation is manifest, mCCL8 is the only T cell-attracting chemokine that is significantly induced in sensitized skin, and its expression is several folds higher than those of CCL1, CCL17 and CCL22. Moreover, trafficking of CCR8⁺ T_H2 cells, which are enriched for IL-5 and the IL-25 receptor, into allergen

sensitized skin is essential for driving skin inflammation, as both IL-5 and IL-25 are cytokines that amplify eosinophilic inflammation (Fig. 4)^{5,112}.

Asthma

The mechanisms of T cell-mediated inflammation have been extensively characterized in human asthma and in mouse models of allergic pulmonary inflammation and have identified CD4⁺ T_H2 cells as being central to the pathogenesis of human asthma. This concept has been established through studies of the specific effects of T_H2 cytokines and the *in vivo* findings that T_H2 cells are sufficient to initiate and drive asthma pathogenesis^{59,77,113,114}. However, it is now well appreciated that other T cell subtypes, such as T_H1, T_H17, T_{reg}, natural killer T (NKT) and innate helper type 2 cells coexist with T_H2 cells and contribute to the pathogenesis of asthma^{113,114}. Furthermore, the plasticity of T_H2 lineage differentiation, such that T_H2 cells may undergo additional differentiation to coproduce IFN- γ or IL-17, has been shown in mouse models of allergic pulmonary inflammation and, for IL-17, in human asthma^{88,89}. Given the chronicity of human asthma, the possibility that various environmental exposures that induce recurrences and exacerbations throughout the course of disease cumulatively modulate the phenotype of an individual's allergic inflammation is not surprising. For example, respiratory viral infections and environmental mold exposure have been shown to be key variables in the exacerbation of allergic asthma^{115–118}.

The clinical presentation of asthma led us to focus our efforts on dissecting the mechanisms that underlie T cell trafficking and inflammation in the lung in the context of the asthmatic response, which can be divided into an early and a late phase¹¹⁹. The early phase of the asthmatic response occurs rapidly (within 5–60 min of allergen exposure) as a result of mast cell degranulation and mediator release and is characterized by airway swelling and bronchoconstriction, which results in a corollary decrease in airway airflow (Fig. 5)¹¹⁹. The early phase response often resolves but is followed several hours (>4) later by a more severe late phase response, which is induced by the infiltration of inflammatory cells, such as T cells and eosinophils in the airways, and is also associated with reduced airway airflow¹¹⁹. The late phase asthmatic response can last for extended periods of time¹²⁰. Moreover, recurrent and constant exposure to inciting allergens drives inflammation and permanent airway remodeling in individuals with chronic asthma¹¹⁹. We first showed that T cell trafficking is necessary for asthmatic inflammation by establishing the essential requirement of GPCR signaling in allergic airway inflammation, for which we used an adoptive transfer model of asthma^{121,122}. T cell trafficking during the early and late phase asthmatic response involves multiple trafficking receptors, which are regulated by both innate and adaptive pathways and are summarized below and reviewed in more detail in ref. 123 (Fig. 5).

Airway mast cells are the innate cells that are crucial for the early phase recruitment of T cells and initiation of the asthmatic response. When sensitized individuals inhale an allergen, pre-existing allergen-specific immunoglobulin E (IgE) leads to the crosslinking of mast cell IgE Fc receptors and the release of T_H2-type effector cytokines, inflammatory mediators, leukotrienes, prostaglandins and inflammatory chemokines by mast cells into the airways (Fig. 5). Among the leukotrienes released by mast cells, leukotriene B₄ (LTB₄) is rapidly generated within minutes of exposure from membrane lipids and is the lipid chemoattractant ligand for the GPCR leukotriene B₄ receptor 1 (BLT1), which is expressed by T_H1, T_H2 and T_H17 cells and induces their migration (unpublished observations and ref. 124). A deficiency of BLT1 leads to a defect in early T cell accumulation in the airways in a model of allergic pulmonary inflammation that involves active allergen immunization and the generation of allergen-specific IgE^{124,125}. Mast cells also produce the chemokines CCL1, CCL17 and CCL22 (refs. 34,126,127). Mast cell release of CCL1 may be key for early T_H2 cell recruitment through the CCR8 receptor, as was shown in a mast-cell-dependent model

of chronic allergic inflammation¹²⁶. The prostaglandins released include prostaglandin D₂ (PGD₂), the receptors for which are the GPCRs DP1 and DP2. DP2 is also called CRTH2 (chemo-attractant receptor-homologous molecule expressed on T_H2 cells) and is expressed by human T_H2 cells. PGD₂ induces migration and activation of T_H2 cells through CRTH2, and polymorphisms of CRTH2 are associated with an increased risk for asthma in Chinese children and African Americans but a reduced risk for asthma in German children^{81,128,129}. The rapid kinetics of mast cell–mediator release suggests that the recruitment of T cells in this early phase probably involves lung-resident allergen-specific memory cells.

During the late, T cell–mediated effector phase of asthma, initial T cell recruitment is probably facilitated by allergen- and damage-associated molecular pattern-mediated activation of pattern recognition receptors, such as Toll-like receptors (TLRs) or C-type lectins on innate immune cells, or by direct activation of epithelial cells by allergens. This induces the production of T_H2-promoting cytokines and chemokines by epithelial cells and innate tissue leukocytes and an initial phase of STAT6-independent recruitment of a small number of allergen-specific T cells into the lungs¹²¹. The kinetics of T cell recruitment in this initial phase suggests that it may also involve lung-resident allergen-specific memory and effector cells. For example, TLR activation and allergen exposure are reported to induce CXCL10 and CCL20 production by macrophages and epithelial cells^{123,130}. The cognate receptors of CXCL10 and CCL20, CXCR3 and CCR6, respectively, are expressed by human T cells that infiltrate the lungs during allergic inflammation, particularly the airways 24 h after allergen challenge^{49,131,132}. Moreover *Ccr6*^{−/−} mice have diminished airway hyper-responsiveness and allergic inflammation, and adoptive transfer of *Ccr6*^{+/+} T cells into *Ccr6*^{−/−} mice increases allergic lung inflammation^{133,134}. Additionally, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) enhances the production of CCL20 by epithelial cells, perpetuating allergic inflammation through increased recruitment of CCR6⁺ memory and effector T_H2 cells into the airways¹³⁵. Likewise, findings with *Cxcl10*^{−/−} and CXCL10 transgenic mice suggest that CXCR3⁺ T cell recruitment enhances allergic pulmonary inflammation¹³⁶.

After the initial trafficking of T cells into the airways, T_H2 cell recruitment into the lungs is markedly amplified after T cell activation by mature dendritic cells in the draining lymph node, where T cells also undergo rapid proliferation⁷⁶. The chemokine receptors CCR4, CCR8 and, possibly, CX3CR1 are the likely key chemokine receptors that regulate T_H2 cell recruitment into the lung during this phase. Concentrations of CCR4, CCR8 and their ligands are elevated in the lung or the bronchoalveolar lavage fluid of patients with asthma and in mouse models after allergen challenge^{137–140}. However, deletion of CCR4 and CCR8 receptors in mouse models of asthma and in human studies has yielded conflicting results^{126,141–146}. Thus, aside from in two studies^{126,141}, CCR8 has not been shown to drive T_H2-type effector cell recruitment in models of allergic airway inflammation^{126,141,143,145,146}. Likewise, 24 h after allergen challenge of steroid-naïve subjects with mild asthma, there was no difference in the expression of CCR4 or its ligands in the bronchoalveolar lavage fluid, although CCR4 was required for efficient tissue entry of T_H2 cells in an adoptive transfer model of acute allergic pulmonary inflammation^{49,146}. In a recent study, CCR4⁺ T cells in the peripheral blood positively correlated with asthma severity in a cohort that included subjects with mild asthma as well as steroid-dependent subjects with moderate to severe asthma, and *ex vivo* production of CCL17 was higher in bronchial biopsy explants from subjects with asthma compared to healthy controls¹⁴⁷. Additionally, studies of airway allergen challenge and genome-wide association have implicated CX3CR1 and its ligand CX3CL1 in human asthma^{108,148}. A recent study provided a possible mechanism for this association by showing that CX3CR1 signaling aided T_H2 cell survival and maintenance to drive allergic pulmonary inflammation¹⁰⁷. Facilitating the long-term persistence of allergen-specific memory and effector T cells is

also a mechanism by which the CCR8 pathway may promote chronic allergic inflammation¹⁴⁹.

To define the transcriptional signals that regulate the induction of inflammatory chemokines and amplify T cell recruitment into the asthmatic lung, we used an adoptive transfer model of acute allergic inflammation and showed that it is STAT6 dependent¹²¹. T cell recruitment was dependent on STAT6 expression by a resident lung cell, which we subsequently showed to be from a subset of CD11b⁺CD11c⁺ myeloid pulmonary dendritic cells, concordant with findings from other groups^{150–152}. Thus, in this model of acute asthma, *Stat6*^{−/−} mice had significantly lower production of the T_H2 cell-attracting chemokines CCL17 and CCL22, as well as decreased induction of the eosinophil-attracting chemokines CCL11 and CCL24. Moreover, CCL17, CCL22 and CCL11 were produced in a STAT6-dependent fashion in a 4-week active immunization model of allergic pulmonary inflammation¹⁵³. In contrast, the transcriptional signals that regulate the induction of CCR8 and CX3CR1 in the allergic lung are not as well defined. Lung mCCL8 induction was STAT6 independent in a chronic 4-week active immunization model¹⁵³. With respect to other T helper subsets, it is notable that T_{reg} cells express the chemokine receptors CCR4 and CCR8 and, thus, may be recruited by the release of CCL1 during the early phase asthmatic response and the release of CCL17, CCL22 and mCCL8 during the late phase asthmatic response⁶⁹.

Food allergy

In humans, allergen-specific T_H2 cells are essential for triggering non-IgE-mediated food allergies as well as maintaining type I IgE-mediated allergic responses. In allergic individuals, allergen-specific T cells in the blood proliferate more in response to food allergens compared to in non-allergic individuals, and human milk-specific T cells derived from the duodenum have a dominant T_H2-type cytokine secretion profile^{154,155}. After food challenges, the duodena of symptomatic individuals contain increased numbers of IL-4⁺CD4⁺ T cells associated with IgE⁺ cells that were mostly mast cells despite lacking food-allergen-specific serum IgE¹⁵⁶. With regard to programmed organ-specific trafficking molecules, the integrin $\alpha_4\beta_7$ is selectively increased in lymphocytes stimulated with β -lactoglobulin in children allergic to cow's milk¹⁵⁷. Peach-protein-allergen-specific T cell clones are also selectively enriched for $\alpha_4\beta_7$ and lack expression of CLA¹⁵⁸. Thus food-allergen-specific T cells in humans are imprinted with gut-specific homing receptors. Milk-induced skin urticaria is also a common manifestation of milk allergy in young children, and milk exposure induces symptoms of eczema in individuals with atopic dermatitis^{159,160}. Notably, milk-induced urticaria and atopic eczema are both associated with increased circulating concentrations of allergen-specific T lymphocytes, which express CLA^{159,160}. Additionally, a recent human study found that anaphylactic peanut allergy is associated with an increased frequency in the number of blood IL-5⁺IL-4⁺ peanut-specific T_H2 cells and IgE responses¹⁶¹. Conversely, blood IL-5⁺IL-4⁺ peanut-specific T_H2 cells are associated with IgE-independent allergic eosinophilic gastroenteritis¹⁶¹. Extending these observations, the majority of peanut-allergen-specific blood CD4 T cells express CCR4 in individuals with a history of peanut anaphylaxis and peanut-specific IgE, and peanut-allergen-specific cell lines from these individuals primarily produce IL-4 (ref. 162).

In the mouse, CCR7 expression on T_{reg} cells is crucial for the induction of oral tolerance in the MLN, and T_{reg} cells are directed to home to the gut lamina propria by MADCAM1 (refs. 67,71). In a mast-cell-dependent mouse model of chronic food allergy in which inflammation is induced in the small intestine and manifests as allergic diarrhea, allergen-specific T cells are induced in the MLN and traffic to the small intestine¹⁶³. In this model, increased numbers of T_H2 cytokines and the CCR8 and CCR4 ligands CCL1, CCL17 and CCL22 are upregulated in the inflamed small intestine¹⁶³. In this same model, CCR6 is

crucial for T cell trafficking to the small intestine and for driving IgE-independent T_H2 cell inflammation and allergic diarrhea¹⁶⁴. Thus, chemokine receptors associated with allergic airway inflammation also seem to drive allergic inflammation in the gut.

Therapeutic targeting of leukocyte trafficking in allergy

We suggest that programmed tissue-specific T cell trafficking pathways during immune surveillance and inflammation contribute to the propensity of the skin, gut and lung for developing allergic diseases. Blocking tissue- and inflammation-specific trafficking pathways provides an opportunity for developing new targeted therapies for inflammation and allergic diseases and is actively being pursued (Table 1). Integrins were the first category of trafficking receptors to be targeted for therapy. Efalizumab, an antibody to CD11a that inhibits skin-homing CLA⁺ T cell entry into the skin, was the first migration-inhibitory drug to be approved by the US Food and Drug Administration, and although it was initially approved for the treatment of psoriasis, it was also reported to be effective in some individuals with atopic dermatitis¹⁶⁵. Among the chemoattractant receptors, the first drug to successfully reach phase 3 clinical trials for an inflammatory disease was, in fact, an antagonist for another tissue-specific homing molecule, CCR9, for the treatment of Crohn's disease. With regard to allergic inflammation, based on population-based genetic studies of an association of CCR2 polymorphisms with allergic disease, many companies are actively pursuing inhibitors of CCR2, some of which have recently completed phase 2 trials^{81,128,129,166}. Other chemokine receptors being targeted for anti-allergic therapy are CCR3 and CCR4. An advantage of anti-migration-based therapy is that the likelihood of toxicity is less than that of immunosuppressive therapy. However, a caveat of extended anti-integrin-based therapies has been an unpredicted increased risk for developing fatal progressive multifocal leukoencephalopathy¹⁶⁷.

In developing therapies based on anti-chemokine receptors, as we highlight in this review, the kinetics of inflammation-driven chemokine induction and T cell chemokine receptor expression during chronic allergic disease dictates the relative roles of different ligand-receptor pairs during distinct phases of disease and in different compartments. Large pre-existing pools of tissue-resident allergen-specific memory T cell pools also probably influence migration-inhibitor-based therapies. Though classical T_H2 cells are the main orchestrators of allergic inflammation through the production of T_H2 effector cytokines, other T helper subsets contribute to allergic inflammation. These factors reflect the importance of multiple T cell trafficking receptor pathways in allergic inflammation. Thus, the strategic design of new therapeutic agents directed against trafficking-receptor pathways for the treatment of allergic inflammation requires an appreciation of these multiple factors.

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Figure 1.

Generation of allergen-specific effector and memory T cells during primary immune responses at the epithelial barrier. During the primary immune response to allergens, disruption of the epithelial barrier leads to epithelial cell production of cytokines, such as TSLP, IL-25 and IL-33. Allergens and other inflammatory cues in the presence of TSLP, IL-25 and IL-33 induce dendritic cell (DC) maturation and trafficking to tissue draining lymph nodes (LN) where dendritic cells activate naive T (T_N) cells to differentiate into T_H2 -type effector (T_{EFF}) cells. Allergen-specific T_{EFF} cells undergo clonal proliferation in the lymph nodes, and T_{EFF} cells exit the lymph nodes through efferent lymphatics. T_{EFF} cells re-enter the systemic circulation through the thoracic duct and enter inflamed tissue through postcapillary venules. The majority of T_{EFF} cells eventually die, but a minority differentiate into memory T (T_M) cells several weeks after the resolution of inflammation. Depending on

the profile of trafficking receptors expressed, different subsets of T_M cells perform distinct types of immune surveillance in the steady state. Naive T cells and central memory T (T_{CM}) cells equipped with L-selectin (CD62L) and the chemokine receptor CCR7 have restricted and specific access to secondary lymphoid tissue through specialized high endothelial venules (HEVs), which express their respective ligands (PNAd and CCL21). T cells recirculate between lymphoid tissue and blood. Effector memory T (T_{EM}) cells primarily recirculate between the blood and peripheral tissue. T_{RM} cells persist in peripheral tissue and do not recirculate. TSLPR, TSLP receptor; IL-33R, IL-33 receptor.

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Figure 2.

Tissue-specific imprinting and steady-state programmed memory T cell trafficking to atopy-prone organs. Dendritic cells of the skin and the gut imprint T cells during the primary immune response to express trafficking receptors that enable tissue-specific homing. Skin T_H17 cells express CLA, CCR10, CCR4 and CCR8, which enable skin T_H17 cell entry into the skin in the steady state, as postcapillary venules in the skin express CCL17, E-selectin and CCL1 (the respective ligands for CCR4, CLA and CCR8) and epidermal cells express CCL27 (the ligand for CCR10) and mCCL8 (the ligand for CCR8 in the mouse). Gut T_H17 cells are programmed to express CCR9 and $\alpha_4\beta_7$, which enable the entry of gut T_H17 cells into the small intestine through postcapillary venules that express CCL25 and MADCAM1,

which are the respective ligands for CCR9 and $\alpha_4\beta_7$. Skin- and gut-specific programmed lymphocyte homing pathways are well characterized in human and mouse studies. Human studies also suggest that programmed tissue-specific homing of lung T_{EM} cells may also occur.

Figure 3.

Chemokine receptors associated with CD4⁺ helper T cell subsets. **(a)** During the primary immune response, cytokines (indicated above the arrow) and transcription factors (T-bet, GATA3 and ROR- γ T) instruct naive T cells to differentiate into T_H cell subsets. After TCR activation, specific cytokines derived from the innate immune system and unique master transcription factors direct naive CD4 T_H cells to differentiate into T_H1, T_H2, T_H17, T_{reg} and T_{HH} cell subsets. Differentiated T_H cell subsets produce lineage-specific effector cytokines and express characteristic chemokine receptors. **(b)** After recall stimulation with an antigen, allergen-specific memory T_H2 cells rapidly produce higher amounts of effector

cytokines, such as IL-4, on rechallenge with the cognate allergen as compared to naive T cells. Repeated allergen-induced T_H2 cell differentiation induces a highly differentiated, CCR8⁺IL-5^{hi} T_H2 cell subset that coexpresses the indicated receptors. Memory T_H2 cells may not be fixed in differentiation along the T_H2 lineage and may adopt features of T_H17 and T_H1 cells on rechallenge with allergen in the context of inflammatory cues derived from fungi or viruses, respectively. TGF- β , transforming growth factor β ; IL-25R, IL-25 receptor.

Figure 4.

Trafficking of T_H2 cell subsets into the skin during the acute and chronic phases of atopic dermatitis. During the acute phase of atopic dermatitis, the initiation of inflammation is dependent on T_H2 cell entry into inflamed skin by CCR4 and the CCR4 ligand CCL17, which is upregulated in inflamed postcapillary venules. During the chronic phase of atopic dermatitis, the pool of allergen-specific skin tissue T_{RM} cells is increased as compared to in the acute phase, and these allergen-specific T_{RM} cells can initiate inflammation independent of CCR4-dependent T_H2 cell entry from the blood. Repeated prior allergen exposure also leads to the *in vivo* generation of the more differentiated $CCR8^{+}IL-5^{hi}$ T_H2 cell subset in the chronic phase. Allergen challenge induces production of the CCR8 ligand, mCCL8, in the

skin. mCCL8-dependent trafficking of L-5^{hi} CCR8⁺ T_H2 cells into the skin drives eosinophilic skin inflammation in the chronic phase of atopic dermatitis in the mouse model.

Figure 5.

Chemokine-regulated T_H cell trafficking into the lung during the early and late phases of the asthmatic response. During the early phase allergic airway response (left), allergen-IgE complexes stimulate airway mast cells to degranulate and release acute mediators such as histamine, tumor necrosis factor α (TNF- α), LTB $_4$, PGD $_2$ and the chemokine CCL1. LTB $_4$, PGD $_2$ and CCL1 recruit T_H2 cells into the airways through BLT1, CRTH2 and CCR8, respectively. T lymphocyte trafficking during the late phase allergic airway response (right) is facilitated by innate cells, such as macrophages and myeloid dendritic cells (mDCs). Allergen-induced TLR activation induces macrophage and epithelial cell release of chemokines such as CXCL10 and CCL20. These chemokines recruit an initial wave of T

cells into the airways through their receptors, CXCR3 and CCR6. IL-4 and IL-13 produced by activated lung allergen-specific T_H1 cells stimulate mDCs to release the chemokines CCL17 and CCL22 in a STAT6-dependent fashion. These chemokines amplify the subsequent recruitment of T_H2 effector cells, which are generated in lung draining lymph nodes, into the airways from the circulation by the T_H2 cell receptor CCR4. IL-4 and IL-13 also induce the differentiation of alternatively activated macrophages, which produce CCL17 to promote CCR4-dependent T_H2 cell recruitment. CCR8 and CX3CR1 are also probably involved in T cell recruitment into the lung during the late phase allergic airway response. CCR8 and CX3CR1 are implicated in human asthma and in mouse models of airway inflammation. The CCR8 ligand mCCL8 is upregulated in mouse models of allergic airway inflammation, but the cellular sources of mCCL8 in the lung have not been defined. The CX3CR1 ligand, CX3CL1, is induced in airway smooth muscle cells, lung endothelium and epithelial cells after allergen challenge.

Table 1

Drugs in development or currently available that inhibit leukocyte migration

Target molecule	Target cell	Compound or drug	Company	Clinical indication and stage of development
CRTH2 (DP2)	T cell, eosinophil and basophil	QAW039, oral antagonist	Novartis	Moderate to severe asthma with sputum eosinophilia; phase 2, currently recruiting
		ADC3680B, oral antagonist	Pulmagen	Partly controlled mild to moderate atopic asthma; phase 2 completed February 2012
		MK-7246, oral antagonist	Merck	In development
		AZD1981, oral antagonist	AstraZeneca	In development
		OC000459, oral antagonist	Oxagen	In development
		AM156, topical antagonist	Amira	Allergic conjunctivitis; in development
		Antagonist	Pfizer/Wyeth	In development
		Antagonist	Millenium	In development
CRTH2 and DP1	T cell, eosinophil and basophil	AMG 853, oral antagonist	Amgen	Asthma; phase 2 completed March 2011
		AMG-009, oral antagonist	Amgen	Asthma and allergic rhinitis; phase 1 planned
CCR3	Eosinophil	GW-766904, oral antagonist	GlaxoSmithKline	Mild to moderate asthmatics with sputum eosinophilia; phase 2, currently recruiting
CCR4	T cell	KW-0761, intravenous antibody	Kyowa Hakko	Allergic rhinitis and healthy volunteers; phase 1 completed
			Kyowa Hakko	Adult T cell leukemia-lymphoma; phase 2 completed April 2011
			Amgen	Non-oncology, asthma and inflammatory indications; in development
		Antagonist	Astellas	In development
		Antagonist	Bristol-Meyers Squibb	In development
CCR9	T cell	GSK1605786A	ChemoCentryx	Crohn's Disease; phase 1 and 2 completed
		Oral antagonist	GlaxoSmithKline	Crohn's Disease; phase 3 recruiting
LFA1 (CD11a-CD18; $\alpha_L\beta_2$ integrin)	T cell	Efalizumab, subcutaneous antibody	Genentech	US Food and Drug Administration (FDA) approved in 2003 for treatment of moderate to severe psoriasis. Voluntarily withdrawn in 2009 because of association with fatal progressive multifocal leukoencephalopathy (PML)
VLA-4 ($\alpha_4\beta_1$ integrin)	T cell	Natal izumab, intravenous antibody	Biogen Idec	FDA approved in 2004 for relapsing-remitting multiple sclerosis. FDA black box warning: increased risk of PML. FDA approved in 2008 for moderate to severe Crohn's disease