

Allergic airway inflammation: key players beyond the Th2 cell pathway

Koichi Hirose | Arifumi Iwata | Tomohiro Tamachi | Hiroshi Nakajima 

Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, Chiba, Japan

Correspondence

Dr. Hiroshi Nakajima, Department of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University, Inohana, Chiba City, Japan.

Email: nakajimh@faculty.chiba-u.jp

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Summary

Allergic asthma is characterized by eosinophilic airway inflammation, mucus hyperproduction, and airway hyperreactivity, causing reversible airway obstruction. Accumulating evidence indicates that antigen-specific Th2 cells and their cytokines such as IL-4, IL-5, and IL-13 orchestrate these pathognomonic features of asthma. However, over the past decade, the understanding of asthma pathogenesis has made a significant shift from a Th2 cell-dependent, IgE-mediated disease to a more complicated heterogeneous disease. Recent studies clearly show that not only Th2 cytokines but also other T cell-related cytokines such as IL-17A and IL-22 as well as epithelial cell cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are involved in the pathogenesis of asthma. In this review, we focus on the roles of these players beyond Th2 pathways in the pathogenesis of asthma.

KEYWORDS

allergic airway inflammation, dendritic cell, IL-22, IL-9, ILC2, Th17 cell

1 | INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, which is characterized by recurrent episodes of airway obstruction, airway hyperresponsiveness (AHR) to non-specific stimuli, mucus hyperproduction, and airway remodeling.^{1,2} In many cases, the disease activity can be controlled by inhaled corticosteroid (ICS) or ICS combined with long-acting β_2 -adrenergic agonists, but in some cases which correspond to severe asthma or difficult asthma, the symptoms are refractory to these standard treatments, and often lead to emergency visit or hospitalization.

The classic view of asthma as a Th2 cell-mediated disease is based on the fact that the pathology of asthma is characterized by infiltration of inflammatory cells such as eosinophils, mast cells, and activated CD4⁺ T cells.^{1,2} Moreover, these infiltrating CD4⁺ T cells express Th2 cytokines, such as IL-4, IL-5, and IL-13,^{3,4} which mediate many aspects of allergic inflammation. In accordance with these findings, GATA3, which is an essential transcription factor for Th2 cell

development, is expressed at high levels in CD4⁺ T cells isolated from asthmatic airways, whereas T-bet, a master regulator of Th1 cell development, is attenuated.^{5,6}

Animal studies further underscore the hypothesis that Th2 cells and their cytokines are crucial for the development of allergic airway inflammation, and help to clarify the mechanisms by which Th2 cells and their cytokines promote these pathological changes. When antigen-specific Th2 cells are transferred into naïve mice and activated by inhaled antigens in the airways, most of asthmatic responses such as eosinophilic inflammation, mucus hyperproduction, and AHR can be provoked in the mice.⁷⁻⁹ Consistently, the inhibition of GATA3 activity in CD4⁺ T cells, which results in the suppression of Th2 cytokine production, is sufficient to attenuate the development of allergic airway inflammation.¹⁰ The importance of Th2 cytokines is also supported by the fact that mice overexpressing individual Th2 cytokines in the airways exhibit characteristic features of allergic inflammation,¹¹⁻¹³ whereas mice deficient in Th2 cytokines such as IL-5 and IL-13 cannot develop allergic inflammation in response to inhaled allergens.¹⁴⁻¹⁶ These studies support the notion that antigen-specific Th2 cells and their cytokines are essential and sufficient for the induction of pathophysiological changes associated with asthma.

However, over the last decade, the understanding of asthma pathogenesis has made a significant shift from a Th2 cell-dependent, IgE-mediated disease to a more complicated heterogeneous disease with many endotypes.¹⁷ This concept is further supported by recent findings that not only Th2 cytokines but also other T cell-related cytokines such as IL-17A and IL-22 are expressed in the airways of asthma.¹⁸ Furthermore, Th2-biased airway inflammation is observed in only half of patients with asthma,¹⁹ and clinical trials with antibodies against Th2 cytokines have shown therapeutic effects only in a particular subset of patients.²⁰ Meanwhile, recent studies have shown that epithelial cell-derived cytokines and their responding cells such as dendritic cells (DCs) and innate lymphoid cells (ILCs) play an important role not only in the initiation of allergic responses but also in the effector phase of allergic inflammation.¹ These findings suggest that although Th2 cells and their cytokines play major roles, there should be more players involved in the development of asthma. In this review, we focus on the roles of these supporting players in the pathogenesis of asthma.

2 | ROLE OF TH17 CELLS IN ALLERGIC AIRWAY INFLAMMATION

Recent cluster analyses have revealed that asthma is a heterogeneous disease with many phenotypes/endotypes and that a subset of asthmatic patients who have neutrophilic airway inflammation shows a severe phenotype.¹⁷ Neutrophilic inflammation is a hallmark of inflammation mediated by CD4⁺ T cells producing IL-17A (Th17 cells), suggesting that Th17 cells and their cytokines including IL-17A play a role in this subtype of asthma.

2.1 | IL-17 and Th17 cells

IL-17, also known as IL-17A, has been identified as one of CD4⁺ T cell-derived cytokines.²¹ Subsequently, CD4⁺ T cells that produce IL-17A, referred to as Th17 cells, have been shown to constitute a distinct lineage from classical Th1 and Th2 cells.²¹ In mice, TCR stimulation in the presence of TGF- β and IL-6 induces naïve CD4⁺ T cells to differentiate toward Th17 cells, which express transcription factors retinoic acid-related orphan receptor (ROR) γ t and ROR α and produce IL-17A and IL-17F, along with IL-21 and IL-22.²¹ Initially, IL-23 was believed to be required for Th17 cell polarization; however, subsequent studies suggest that IL-23 is dispensable for polarization toward Th17 cells but essential for supporting memory/pathogenic Th17 cells.²² In humans, Th17 cell development can be induced by IL-1 β and IL-23 and further enhanced by the presence of IL-6.²³ Th17 cells are thought to play a key role in inflammation, autoimmunity, and host defense against extracellular bacteria and fungi.²⁴

2.2 | IL-17 and Th17 cells in patients with asthma

The role of IL-17A/F and Th17 cells in asthma is an area of concern. It has been reported that the levels of IL-17A and IL-17F in sputum

are elevated in patients with asthma^{18,25} and that increased levels of IL-17A are associated with neutrophilic inflammation, increased AHR, and steroid resistance.^{26–28} Ricciardolo et al.²⁹ have reported that IL-17F-expressing cells are abundant in bronchus in severe asthma with frequent exacerbation. In addition, Pene et al.³⁰ have shown that lung tissues of asthmatics contain significant numbers of Th17 cells that produce IL-22 as well as IL-17A. Furthermore, a genetic study has revealed that polymorphism of IL-17F gene that results in a loss of function is inversely correlated with asthma risk.³¹ The importance of Th17 cells in asthma is further supported by a clinical study showing that increasing number of Th17 cells in the peripheral blood is correlated with the severity of childhood asthma.³² Based on the gene expression profiles of bronchial biopsies, Choy et al. have identified three distinct subgroups of asthmatics; Th2-high asthma, Th17-high asthma, and Th2/Th17 low asthma. Among them, Th17-high asthma is associated with a steroid-dependent, most severe phenotype.³³ These findings indicate that Th17 cell-derived IL-17A and IL-17F are important mediators for neutrophilic inflammation and a severe phenotype in asthma.

However, contrary to expectation, anti-IL-17 receptor A (IL-17RA) monoclonal antibody brodalumab, which inhibits the function of IL-17A and IL-17F, showed only a little therapeutic benefit for moderate to severe asthma.³⁴ The limited effects of brodalumab can be explained by the reciprocal regulation of Th2 and Th17 responses in which a blockade of Th17 pathway is compensated by Th2 pathway, and vice versa.³³ Further studies are needed to identify a subgroup of asthmatic patients who gain potential therapeutic benefits of IL-17RA blockade and to explore the possibility of combined therapy with anti-Th2/Th17 cytokines.

Recent studies have shown that under inflammatory conditions, Th17 cells can produce cytokines that are typically produced by either Th1 cells or Th2 cells.³⁵ Consistently, a considerable proportion of CD4⁺ T cells in the bronchoalveolar lavage fluid (BALF) or peripheral blood in asthmatic patients has been shown to produce both IL-17A and Th2 cytokines such as IL-4, IL-5, and IL-13.^{36–38} These dual positive Th2/Th17 cells induce chemokine expression in lung epithelial cells more efficiently than Th2 cells or Th17 cells.³⁶ Furthermore, asthmatic patients who have Th2/Th17 cells in the BALF show a severe phenotype with strong airway obstruction and AHR as compared to those who have solely Th2 cells.³⁸ The unique functions and the increased numbers of dual positive Th2/Th17 cells in the BALF in severe asthmatics suggest that Th2/Th17 cells play a crucial role in the pathogenesis of asthma.

2.3 | Roles of Th17 cells in murine asthma models

Given that IL-17A is suggested to be involved in the pathogenesis of asthma, we have analyzed the role of IL-23-Th17 cell axis in murine asthma models. We found that mRNA for IL-23 is expressed in the lung upon antigen inhalation and that neutralization of IL-23 attenuates not only neutrophilic inflammation but also Th2 cytokine production and eosinophilic inflammation in the airways in antigen-challenged mice.³⁹ We also found that transfer of antigen-specific

Th17 cells causes neutrophilic inflammation but not eosinophilic inflammation upon antigen inhalation; however, importantly, when co-transferred with antigen-specific Th2 cells, Th17 cells promote Th2 cell-mediated eosinophilic airway inflammation by enhancing the expression of eotaxin-1 and eotaxin-2.³⁹ Furthermore, McKinley et al.⁴⁰ have shown that Th17 cell-mediated neutrophilic airway inflammation and AHR are steroid-resistant. Pathogenic roles of Th17 cells in allergic airway inflammation are further supported by the fact that antigen-sensitized and -challenged ROR γ t transgenic mice show increased IL-17A expression, neutrophilic inflammation, and steroid insensitivity.⁴¹ The link between steroid insensitivity and Th17 cells is also underscored by the fact that steroid treatment fails to inhibit IL-17-mediated inflammation and chemokine expression.³³ Taken together with the clinical study showing a positive correlation between IL-17A levels and steroid insensitivity in asthma, these data indicate the involvement of Th17 cells in the mechanisms underlying steroid insensitivity in severe refractory asthma.

2.4 | Regulation of Th17 cell development in allergic airway inflammation

In addition to ROR γ t, a key transcription factor for Th17 cell development, series of studies have revealed that several transcription factors are involved in the development of Th17 cells.⁴² Regarding the mechanism underlying Th17 cell differentiation in asthma models, it has been shown that serum amyloid A enhances Th17 cell responses in the lung through IL-1 production,⁴³ suggesting that inflammasome-activating molecules are capable of inducing Th17 cell differentiation. In addition, C-type lectin receptors, Dectin-1 and Dectin-2, which recognize fungal cell wall components β -glucan and α -mannan, respectively, enhance IL-23 production from DCs in response to unknown components in house dust mite (HDM) allergens and promote Th17 cell differentiation.^{44–47} Consistently, a large number of Th17 cells and steroid insensitivity are observed in mice sensitized by antigens together with β -glucan,⁴⁶ suggesting that signals through C-type lectin receptors induce Th17 cell differentiation. Moreover, Watanabe et al.⁴⁸ have shown that Menin, a component of trithorax complex, is required for differentiation and maintenance of Th17 cells and neutrophilic airway inflammation but not for the development of Th1 cells and Th2 cells, indicating the involvement of Menin-mediated epigenetic modifications in Th17 cell differentiation. Concerning the inhibitory mechanisms of Th17 cell differentiation in asthma models, we have shown that mice injected with T-bet-deficient CD4⁺ T cells exhibit not only enhanced Th2 cell-mediated eosinophilic airway inflammation but also enhanced IL-17A-mediated neutrophilic airway inflammation,⁴⁹ suggesting that T-bet antagonizes the differentiation of Th17 cells as well as Th2 cells in asthma models.

2.5 | Role of IL-17 in allergic airway inflammation

Studies examining the roles of IL-17A have yielded conflicting results. Hellings et al.⁵⁰ have reported that IL-17A neutralization

prior to antigen challenge attenuates neutrophilic airway inflammation. Consistently, we have shown that antigen-induced neutrophilic airway inflammation but not eosinophilic airway inflammation is attenuated in IL-17A-deficient mice,³⁹ indicating that IL-17A is involved in the induction of neutrophilic but not eosinophilic inflammation. In contrast, other groups have shown that exogenous IL-17A suppresses eosinophilic airway inflammation, whereas neutralization of IL-17A augments eosinophilic airway inflammation.^{50,51} On the other hand, another study has shown that IL-17A synergizes with Th2 cytokines to enhance the expression of eotaxin-1,⁵² an important chemokine for eosinophil recruitment into the airways. The discrepancy among these studies may result from the differences in experimental conditions, such as timing of IL-17A administration and inhibition.

A direct effect of IL-17A on the induction of AHR has also been reported. McKinley et al.⁴⁰ have shown that chronic expression of IL-17A in the lung by adenovirus-mediated gene transfer is sufficient to induce AHR. In addition, Pichavant et al.⁵³ have shown that IL-17A production from NKT cells is essential for ozone-induced AHR. Kudo et al.⁵⁴ have also shown that IL-17A but not IL-17F produced by Th17 cells has a direct effect on muscle contraction, resulting in antigen-induced AHR. These findings indicate that IL-17A plays an important role in the pathophysiology of asthma by promoting AHR.

3 | ROLE OF TH22 CELLS IN ALLERGIC AIRWAY INFLAMMATION

3.1 | IL-22 and Th22 cells

IL-22 is a member of the IL-20 cytokine subfamily, which consists of IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29.⁵⁵ IL-22 was initially recognized as a Th1 cytokine.⁵⁶ However, subsequent studies have revealed that among murine CD4⁺ T-cell subsets, Th17 cells are the major producers of IL-22,⁵⁷ thereby considering IL-22 as a Th17 cytokine. In contrast, in human CD4⁺ T cells, most of IL-22-producing CD4⁺ T cells do not produce signature cytokines such as IFN- γ , IL-4, and IL-17 and do not express T-bet or ROR γ t.^{58,59} These IL-22-producing CD4⁺ T cells are now considered as an independent lineage of CD4⁺ T cells, namely Th22 cells.

Human Th22 cells are characterized by the expression of chemokine receptors CCR4 and CCR10.^{58,59} As ligands for these chemokine receptors are strongly expressed in the skin, Th22 cells are abundant in the skin but rare in peripheral blood. In mice, IL-22-producing CD4⁺ T cells which correspond to human Th22 cells can be found *in vivo*, as we have shown that one-third of IL-22-producing CD4⁺ T cells in the lung in ovalbumin (OVA)-induced asthma models do not produce IFN- γ , IL-4, or IL-17.⁶⁰ However, it remains unclear whether murine Th22 cells are an independent lineage of CD4⁺ T cells as human Th22 cells. In addition to CD4⁺ T cells, some CD8⁺ T cells also produce IL-22⁶¹; however, physiological importance of IL-22-producing CD8⁺ T cells remains to be determined. Recently, a series of innate immune cells including $\gamma\delta$ T cell, NKT cells, and NKp46⁺ NK-like cells have been shown to produce IL-22.⁶² Further studies are needed to clarify the

relative importance of these IL-22-producing innate cells in disease and homeostatic conditions.

3.2 | IL-22 and Th22 cells in human asthma

It has been reported that the levels of IL-22 mRNA in peripheral blood mononuclear cells^{63–65} as well as the levels of IL-22 protein in sera^{66,67} are elevated in patients with asthma. Pennino et al.⁶⁵ have reported that the majority of IL-22-producing cells in the lung in patients with asthma are CD4⁺ T cells. Further analysis of IL-22-producing CD4⁺ T cells in the lung revealed that although 40% of IL-22-producing cells co-produce IFN- γ , 15% of IL-22-producing cells produce neither IFN- γ nor IL-17,⁶⁵ suggesting the involvement of Th22 cells in IL-22 production in asthma. Regarding the function, IL-22 has been shown to inhibit inflammatory responses induced by IFN- γ .⁶⁵ Furthermore, several groups have shown the protective roles of IL-22 against pathogens at mucosal surfaces.^{68,69} Although the roles of IL-22 and Th22 cells in human asthmatic patients remain largely unknown, these findings suggest that IL-22 may provide some benefits in asthma especially in infection-induced asthma exacerbations.

3.3 | Roles of IL-22 and Th22 cells in murine asthma models

To clarify the roles of IL-22 in allergic airway inflammation, we examined the effect of a neutralizing anti-IL-22 antibody on antigen-induced airway inflammation in asthma models. We found that the administration of anti-IL-22 antibody significantly enhances antigen-induced eosinophilic airway inflammation, Th2 cytokine production in the airways, and AHR, whereas intranasal administration of recombinant IL-22 attenuates antigen-induced eosinophilic airway inflammation.⁶⁰ Consistently, Taube et al.⁷⁰ have reported that antigen-induced eosinophilic airway inflammation is enhanced in IL-22-deficient mice. Moreover, it has been demonstrated that enforced expression of IL-22 by gene transfer suppresses eosinophilic airway inflammation and Th2 cytokine production in the airways.⁷¹ These findings suggest that IL-22 has a protective role against the development of antigen-induced eosinophilic airway inflammation. On the other hand, Besnard et al.⁶⁷ have shown that IL-22 plays a crucial role in the initiation of immune responses induced by subcutaneous sensitization in OVA-induced asthma models. Taken together, it is suggested that IL-22 has a double-edged role in allergic airway inflammation.

Regarding IL-22 producers in asthma models, as mentioned earlier, we have shown that CD4⁺ T cells are the major cellular source of IL-22 in the lung and that one-third of IL-22-producing CD4⁺ T cells correspond to Th22 cells in a classical OVA-induced asthma model on a BALB/c background.⁶⁰ In contrast, Taube et al.⁷⁰ have shown that IL-22 is predominantly produced by ILCs in the lung in mice challenged with OVA in unsensitized OVA-specific T-cell receptor transgenic (OT-II) mice on a C57BL/6 background. It remains unclear how protein allergen such as OVA induces IL-22 production in ILCs that lack specific antigen receptors.

4 | ROLES OF OTHER HELPER T-CELL SUBSETS IN ASTHMA

Recent studies have shown that other helper T-cell subsets including Th1 cells, Th9 cells, and follicular helper T (Tfh) cells are involved in asthma pathogenesis, whereas regulatory T (Treg) cells are involved in the suppression of allergic diseases including asthma.

4.1 | Th1 cells in allergic airway inflammation

The levels of IFN- γ , a representative Th1 cell-derived cytokine, are elevated during asthma exacerbation, and considerable numbers of Th1 cells are detected in the airways of asthmatics,^{72,73} suggesting that Th1 cells are also involved in the pathogenesis of asthma. The early studies have shown that Th1 cells alone do not induce any features of asthma, and that IFN- γ inhibits Th2 cell-mediated eosinophilic inflammation, mucus production, and AHR.^{74–77} Meanwhile, one of these studies has shown that Th1 cells provoke neutrophilic inflammation in the airways,⁷⁶ which is often associated with severe asthma. In contrast, it has been shown that Th1 cells enhance Th2 cell-mediated allergic inflammation and AHR, presumably by enhancing the recruitment of Th2 cells into the lung in an antigen-non-specific mechanism.^{78,79} Raundhal et al.⁸⁰ have also shown the involvement of IFN- γ and Th1 cells in the pathogenesis of severe asthma. These findings suggest that the impact of Th1 cell-IFN- γ axis on Th2 cell-mediated airway inflammation is modulated by the balance between its suppressive effect on Th2 cell differentiation/activation and its promoting effect on the recruitment of differentiated Th2 cells into the airways.

4.2 | Th9 cells in allergic airway inflammation

IL-9 was thought to be produced by Th2 cells; however, recent studies have identified a new helper T-cell subset, namely Th9 cell, which preferentially produces considerable amounts of IL-9.^{81,82} Consistent with a previous finding that constitutive overexpression of IL-9 in lung reproduces a part of pathological features of asthma,¹² several murine studies have indicated that Th9 cells play substantial roles in the pathogenesis of asthma.^{83–86} In addition, a recent clinical study has shown that the number of Th9 cells is increased in the peripheral blood in patients with asthma as compared with that in control subjects.⁸⁷ These results suggest that Th9 cells also play a role in the pathogenesis of asthma.

4.3 | Tfh cells in allergic airway inflammation

Tfh cells, which express CXCR5 to localize to germinal center in secondary lymphoid organs, are specialized providers of T cell help to B cells.^{88–90} Thereafter, they are thought to be an independent lineage of helper T cells, which are essential for inducing affinity maturation and isotype switching of B cells.⁹¹ In addition, a recent study has shown that Tfh cells play an essential role in IgE production for protein allergens.⁹² Furthermore, Tfh cells have been shown to differentiate

into pathogenic Th2 cells that produce IL-4 and IL-13 and play a pathogenic role in asthma.⁹³ Although these murine studies suggest the involvement of Tfh cells in the pathogenesis of allergic airway inflammation, its importance in the pathogenesis of human asthmatics remains largely unknown.

4.4 | Treg cells in allergic airway inflammation

Treg cells have been recognized as CD4⁺ T cells that suppress immune responses and maintain self-tolerances.⁹⁴ The importance of Treg cells in the prevention of allergic diseases is evident from the fact that patients who have a mutation in FOXP3 gene, an essential transcription factor for Treg cell differentiation, develop severe allergic diseases.⁹⁵ It is well established that Treg cells are divided into two subsets: thymus-derived Treg cells and peripheral Treg cells. Among them, peripheral Treg cells have been shown to be essential for the prevention of allergic diseases in the lung.⁹⁶

5 | ROLE OF DENDRITIC CELLS IN ALLERGIC AIRWAY INFLAMMATION

5.1 | DC subsets

DCs have a strong ability to activate naïve T cells, thereby playing a critical role in the initiation of adaptive immunity.^{97–100} DCs are comprised of three major subsets, classical DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs). cDCs can be further subdivided into two major subsets, recently renamed cDC1s and cDC2s, by tissue distribution patterns, cell surface markers, and dependency on specific transcription factors.^{97–100} cDC1s, called *Batf3/Irf8*-dependent DCs, recognize intracellular pathogens and play central roles in type 1 immune responses and cross-presentation to CD8⁺ T cells,^{100,101} whereas cDC2s, called *Irf4*-dependent DCs, induce type 2 immune responses against parasites by activating Th2 cells.¹⁰² cDC2s also sense some extracellular bacteria and initiate type 3 immune responses through the activation of Th17 cells and type 3 ILCs (ILC3s).^{103,104} Thus, each cDC subset functions as the gatekeeper of the immune responses by sensing a particular type of pathogens and activating innate and adaptive immune responses. On the other hand, pDCs express Siglec-H, bone marrow stromal antigen-2, Ly6C, and B220 and produce large amounts of type I IFNs in response to viral infection.^{97–100} Both cDCs and pDCs are derived from bone marrow progenitor cells, whereas moDCs, also known as inflammatory DCs, are differentiated from monocytes under inflammatory circumstances.^{97,105}

5.2 | Role of DCs in Th2 cell induction in asthma

Importance of DCs in the induction of allergy has been proven by a series of murine studies. When antigen-loaded bone marrow-derived DCs or splenic cDCs are injected into the lungs and activated by the same antigen, they cause a Th2 cell-driven eosinophilic inflammation and AHR.^{106,107} In addition, repeated injections of allergen-pulsed

DCs into the lung induce persistent Th2 cell responses and airway remodeling involving the deposition of the extracellular matrix.¹⁰⁸ It has been demonstrated that induction of Th2 cells, AHR, and goblet cell metaplasia in response to allergens are abolished if lung DCs are depleted at the first exposure to the inhaled allergen in CD11c-diphtheria toxin receptor (DTR)-transgenic mice.¹⁰⁹

In steady-state conditions, lung cDCs mainly consist of two subsets, CD103⁺ cDC and CD11b⁺ cDCs, which represent cDC1s and cDC2s, respectively.^{97–100} pDCs are also found in the lung at a lesser extent. Among the cDC subsets, CD11b⁺ cDCs are thought to be essential for the induction of Th2 responses against allergens. It has been shown that CD103⁺ cDCs and CD11b⁺ cDCs that are sorted and stimulated with allergens induce Th1 and Th2 responses, respectively.¹¹⁰ Similarly, if CD11b⁺ cDCs isolated from lymph nodes of sensitized mice are transferred to naïve recipient mice, they can induce asthmatic responses.¹¹¹ Mesnil et al.¹¹² have also shown that CD11b⁺ cDCs are indispensable for allergic responses to HDM in mice. Severely reduced type 2 responses in CD11c-Cre x *Irf4*^{flx/flx} mice that selectively lack CD11b⁺ cDCs¹¹³ support the notion that CD11b⁺ cDCs are necessary for inducing Th2 cell-driven immune responses. In contrast, depletion of CD103⁺ cDCs using langerin-DTR mice does not abolish the characteristics of asthma, confirming the redundant role of CD103⁺ cDCs in murine asthma models.¹¹¹ Indeed, it has been demonstrated that CD103⁺ cDCs might even be tolerogenic toward inhaled allergens.¹¹⁴ Although these findings implicate that CD11b⁺ cDCs but not CD103⁺ cDCs play an important role in inducing Th2 cell differentiation during the sensitization phase, the precise mechanisms of action are still poorly understood.

5.3 | Role of DCs in the effector phase of allergic airway inflammation

Recent findings indicate that the importance of DCs in the pathogenesis of asthma is not limited to the initiation of Th2 cell responses against allergens but extended to the effector phase of allergic airway inflammation. Using a diphtheria toxin-mediated depletion system, it has been demonstrated that the depletion of CD11c-expressing cells during the effector phase of asthma models prevents eosinophilic airway inflammation and AHR even in the presence of antigen-specific Th2 cells.¹¹⁵ Moreover, it has been shown that reconstitution of DCs at the effector phase restores antigen-induced eosinophilic inflammation and Th2 cytokine production.¹¹⁵ Consistently, Plantinga et al.¹¹¹ have shown that when transferred intratracheally, both CD11b⁺ cDCs and moDCs are capable of inducing Th2 cytokine production and eosinophilic airway inflammation. These findings suggest that in addition to their roles in the initiation of Th2 cell responses, DCs play an important role in amplifying Th2 cell-mediated airway inflammation at the effector phase of asthmatic responses. On the other hand, CD103⁺ cDCs seem dispensable, as the depletion of CD103⁺ cDCs before the antigen challenge has negligible effects on the development of eosinophilic inflammation and Th2 cytokine production.¹¹¹

Regarding the mechanisms of action, it has been shown that when moDCs are activated at the site of eosinophilic inflammation, they

express high levels of costimulatory molecules such as OX40L, CD80, CD86, PDL1, and PDL2.¹¹⁵ In secondary immune responses, DCs have been shown to locate very close to effector T cells and T resident memory (Trm) cells at the site of inflammation,^{116,117} suggesting that DCs may stimulate effector T cells and Trm cells by providing costimulatory signals.^{111,118} Because allergen-specific IgE and IgG1 antibodies bind to DCs through Fc receptors and enhance allergen uptake of DCs in sensitized mice,^{119,120} it is plausible that DCs might further boost Th2 cell responses in an antigen-specific manner. With respect to the roles of DCs beyond the amplification of Th2 cell responses during the effector phase in asthma models, we have shown that moDCs under a Th2 cell-rich environment induce AHR, independently of the induction of allergic airway inflammation,¹²¹ indicating the importance of moDCs in the induction of AHR as effector cells in Th2 cell-driven asthmatic responses.

5.4 | Activation of DCs by epithelial cells

Although DCs can directly sense the environmental factors through pattern recognition receptors (PRRs), recent studies have shown that the epithelial cells play an important role in the activation of DCs upon allergen exposure.^{122,123} As the first-line defense against inhaled antigens, lung epithelial cells are known to express a series of PRRs, including Toll-like receptors (TLRs) and protease-activated receptors. Using bone marrow chimeric mice, several groups have shown that not only TLRs expressed on DCs but also those on non-hematopoietic cells are essential for the development of allergic airway inflammation.^{124–126} Activation of lung epithelial cells by these PRRs results in the production of epithelial cytokines, including IL-25, IL-33, thymic stromal lymphopoietin (TSLP), and GM-CSF, which share the capacity to activate DCs, leading to the development of Th2 cell responses. These findings suggest that epithelial cells provide more than physical barrier function even in allergen-induced asthma possibly through the production of these epithelial cytokines in response to allergens.

6 | EPITHELIAL CELLS AND THEIR CYTOKINES IN ALLERGIC AIRWAY INFLAMMATION

6.1 | Epithelial cells in asthma; beyond the barrier function

Lung epithelium is always exposed to a variety of environmental allergens and pathogens. It protects the lung from these agents by forming a physical and chemical barrier involving secretion of mucus, which captures inhaled allergens and pathogens that can be cleared by the mucociliary transport. However, hyperproduction of mucus is associated with the pathogenesis and severity of asthma.^{122,123} A recent study has shown that Muc5ac, a predominant mucin produced by epithelial cells in asthmatic conditions,¹²⁷ is a central effector for inducing AHR by causing mucous plugging.¹²⁸ In addition, we have shown that IκBNS, one of atypical IκB proteins, in lung epithelial cells induces Muc5ac expression and causes AHR in HDM-induced asthma

models.¹²⁹ These findings suggest that the homeostatic maintenance of lung epithelium is crucial for the prevention of the development of asthma.

Recent studies have shown that in addition to the barrier function, the bronchial epithelium plays a critical role in immune surveillance and proper activation of immune cells to maintain epithelial homeostasis in the response not only to pathogens and other danger substances but also to non-pathogenic allergen.^{123,130} Upon allergen recognition by PRRs, epithelial cells release a variety of cytokines such as IL-25, IL-33, TSLP, and GM-CSF that activate innate immune cells including DCs, basophils, eosinophils, macrophages, and type 2 ILCs (ILC2s).¹³⁰ In addition, triggering of lung epithelial cells by PRRs leads to the release of endogenous danger signals, such as DNA, uric acids, ATP, and high mobility group box 1, some of which have been shown to act as an adjuvant that activates DCs to induce Th2 cell responses.^{131,132} It is assumed that different allergens stimulate these pathways at different contexts, which could be affected by the expression of PRRs, barrier function, cytokine/chemokine production, and immune cell activation. Therefore, epithelial cells seem to be crucial for controlling the consequence of allergen exposure.

Recent studies support the hypothesis that lung epithelial cell-derived cytokines initiate and augment type 2 immune responses in the airways, resulting in the development of asthma.¹³⁰ It is presumed that these epithelial cytokines have both redundant and non-redundant functions in the pathogenesis of asthma by modulating the function of innate immune cells as well as acquired immune cells in the lung. These epithelial cytokines may also have diverse functions in distinct phenotypes/endotypes of asthma in humans. The mechanisms by which epithelial cells produce these cytokines in response to various environmental and microbial stimuli and the roles of these epithelial cytokines in patients with asthma are major unanswered questions in the field.

6.2 | Role of IL-25 in allergic airway inflammation

IL-25, also named IL-17E, is a member of the IL-17 family cytokines.¹³³ A receptor for IL-25 is a heterodimeric receptor composed of IL-17 receptor B (IL-17RB) and IL-17RA.¹³⁴ Regarding IL-25-producing cells, Fort et al.¹³⁵ have shown that IL-25 is mainly produced by highly polarized Th2 cells. Thereafter, in addition to Th2 cells, a variety of cells including activated mast cells, alveolar macrophages, eosinophils, and basophils have been reported to produce IL-25.^{136–138} Epithelial and endothelial cells have also been shown to express IL-25 in humans and mice.^{139–142} Recently, von Moltke et al.¹⁴³ have shown that the majority of IL-25-expressing cells under steady-state conditions are epithelial cells in the intestine by generating IL-25-reporter mice. Furthermore, it has been shown that tuft cells, a rare epithelial cell type in intestinal epithelium, undergo a rapid and extensive expansion and secrete IL-25 following helminth infection, thereby facilitating type 2 immune responses.^{143–145} These results suggest that although some of immune cells can produce IL-25 upon stimulation, epithelial cells are the major cellular source of IL-25 in vivo. The type of lung

epithelial cells that produce IL-25 under asthmatic conditions remains uncertain.

Among IL-17 family cytokines, IL-25 is less homologous to other IL-17 family members¹³³ and the *in vivo* biological activities of IL-25 are markedly different from those described for IL-17A and other IL-17 family members.¹⁴⁶ It has been reported that intraperitoneal injection of purified IL-25 causes eosinophilic infiltration, mucus production, and epithelial cell hyperplasia in the lung by inducing the production of IL-5 and IL-13 from MHC II^{high}CD11c^{dull} lineage-negative cells.¹³⁵ Subsequent studies have revealed that IL-25-responding, lineage-negative cells that induce type 2 immune responses are ILC2s.^{147,148} In addition, multipotent progenitor type 2 cells,^{149,150} type 2 myeloid cells,¹⁵¹ and NKT cells¹⁵² have been reported as IL-25-responding cells that induce type 2 immune responses.

In terms of allergic airway inflammation, we have shown that IL-25 mRNA is expressed in the lung of OVA-sensitized and -challenged mice, and that neutralization of IL-25 by soluble IL-25 receptor suppresses OVA-induced eosinophil and CD4⁺ T cell recruitment into the airways.¹⁴³ We also found that although enforced expression of IL-25 in lung epithelial cells itself fails to induce allergic airway inflammation, the enforced expression of IL-25 significantly enhances OVA-induced Th2 cytokine production, eosinophil and CD4⁺ T cell recruitment, and goblet cell hyperplasia in the airways.¹⁵³ In addition, we have shown that IL-25-mediated enhancement of OVA-induced airway inflammation is inhibited by the depletion of CD4⁺ T cells or by the absence of signal transducer and activator of transcription 6 (STAT6).¹⁵³ Sharkhuu et al.¹⁵⁴ have also shown that IL-25 induces asthmatic responses including Th2 cytokine production, eosinophilic inflammation, mucus hypersecretion, and AHR in wildtype mice but not in IL-13-, IL-4R α -, or STAT6-deficient mice. These findings suggest that Th2 cells are involved in IL-25-mediated asthmatic responses. Using bone marrow chimeric mice with IL-25-deficient mice, Suzukawa et al.¹⁵⁵ have shown that the induction of eosinophilic airway inflammation is dependent on IL-25 produced by airway structural cells but not by immune cells.

Importantly, it has been shown that the expression of IL-25 and its receptor is markedly upregulated in asthmatic conditions.¹³⁸ Cheng et al.¹⁵⁶ have also reported that mRNA levels of IL-25 in bronchial brushing samples are elevated in a subset of asthmatic patients with enhanced AHR, more eosinophilia, higher IgE levels, and higher plasma IL-25 levels, suggesting that IL-25 may contribute to the pathogenesis of Th2-high allergic asthma. Furthermore, Corrigan et al.¹⁴² have shown that IL-25 immunoreactivity is mainly located in epithelial cells, eosinophils, mast cells, and endothelial cells, while IL-17RB immunoreactivity is located in eosinophils, mast cells, endothelial cells, and T cells in bronchial biopsies from patients with asthma. The diverse expression of IL-25 and its receptor suggests the intricate roles of IL-25 in the pathogenesis of asthma.

Interestingly, Corrigan et al.¹⁴² have shown that vascular endothelial cell is the major cell type that expresses IL-17RB in the bronchial mucosa of patients with asthma. Consistently, it has been shown that IL-25 increases endothelial cell proliferation and formation of microvessel structures,¹⁴¹ suggesting that IL-25 may also contribute

to abnormal angiogenesis, one of features of airway remodeling in asthma. In this regard, we found that injection of neutralizing anti-IL-25 antibody inhibits antigen-induced pulmonary arterial wall thickening and resistin-like molecule- α expression in chronic asthma models.¹⁵⁷ Gregory et al.¹⁵⁸ have also reported that administration of anti-IL-25 antibody reduces pulmonary peribronchial collagen deposition, smooth muscle hyperplasia, and recruitment of endothelial progenitor cells in the lungs in asthma models. These findings suggest that IL-25 is involved not only in the induction of allergic airway inflammation but also in the remodeling during asthmatic responses.

6.3 | Role of IL-33 in allergic airway inflammation

IL-33, a member of the IL-1 family cytokines, is mainly produced by intestinal and airway epithelial cells that are exposed to the ambient atmosphere.¹⁵⁹ In addition, keratinocytes, endothelial cells, and smooth muscle cells are shown to produce IL-33.¹⁵⁹ IL-33 is continuously expressed under homeostatic conditions and can be augmented under inflammatory conditions. IL-33 is generally not expressed in hematopoietic cells under homeostatic conditions, but can be induced in macrophages, DCs, mast cells, and monocytes under inflammatory conditions, albeit at lower levels than epithelial cells.¹⁵⁹

IL-33 has been shown to function at two sites, the nucleus and extracellular space, and in two forms, proIL-33 and mature IL-33.¹⁵⁹ IL-33 is stored in the nuclear space as proIL-33 and broken down to mature IL-33 when released by inflammatory stimuli.¹⁵⁹ Several proteases have an ability to process proIL-33 into mature forms of IL-33 and the processing as well as release of proIL-33 seems to be cell lineage-specific.¹⁵⁹ Although cleavage of proIL-33 is not necessary for its bioactivity, the bioactivity of IL-33 can be increased following processing by inflammatory proteases such as neutrophil elastase and cathepsin G which cleave IL-33 within the central domain and generate mature IL-33.¹⁶⁰ Mast cell-derived serine proteases, chymase and tryptase, also cleave IL-33 in the central domain and release active isoforms.¹⁶¹ Similar IL-33-processing activity is found in proteases derived from pathogens as well as pollen, HDM, and fungal allergens.¹⁶² In contrast, processing by caspases inactivates IL-33.¹⁶⁰

Both proIL-33 and mature IL-33 bind to IL-33 receptor consisting of two subunits, IL-1RL1 (called ST2) and IL-1 receptor accessory protein (IL-1RAcP).¹⁶³ The receptor binding results in the activation of NF- κ B and MAPK that induces the production of various cytokines and chemokines or causes cell differentiation and activation, depending on the cell types.^{164,165} The bioactivity of IL-33 is regulated not only by the production and proteolytic processing of proIL-33 but also by the presence of a decoy receptor, soluble ST2.¹⁶⁶ Furthermore, a recent study has shown that the bioactivity of IL-33 is rapidly terminated in the extracellular environment by formation of disulfide bridges, resulting in an extensive conformational change that disrupts the binding to ST2.¹⁶⁷

The representative function of IL-33 is to induce type 2 immune responses, including activation and accumulation of ILC2s,^{168,169} Th2 cells,¹⁷⁰ and M2 macrophages.¹⁷¹ IL-33 also induces the expression of IL-4 and IL-13 and enhances IgE-mediated degradation in basophils.¹⁷²

Cherry et al.¹⁷³ have demonstrated that IL-33 induces eosinophil superoxide anion production and degranulation as potent as IL-5 and increases eosinophil survival. Moreover, interesting functional implications of IL-33 have recently been reported in colonic ST2⁺ Tregs¹⁷⁴ and pathogenic Th2 cells.¹⁷⁵

Several studies have shown that mice administered with recombinant IL-33 develop a marked epithelial cell hyperplasia in the pulmonary and GI tracts, accompanied by eosinophilic infiltration.¹⁵⁹ It has also been shown that IL-33-ST2 axis is important for the development of AHR and airway inflammation in murine asthma models.¹⁵⁹ Moreover, activation of lung ILC2s by IL-33 mediates influenza-induced AHR, independently of adaptive immunity.¹⁷⁶ In asthmatic patients, increased expression of IL-33 in the nuclei of airway epithelial cells has been demonstrated.¹⁷⁷ It has also been reported that IL-33 levels in the BALF and in the sera are higher in patients with asthma than those in healthy controls.^{178,179} Moreover, single nucleotide polymorphisms in IL-33-ST2 pathway are associated with asthma and specific wheezing phenotypes.¹⁸⁰ Taken together, these findings suggest that IL-33-ST2 axis is involved in the pathogenesis of asthma. On the other hand, similar to IL-25, IL-33-ST2 axis has been shown to be required for ILC2-dependent restoration of airway epithelial integrity after influenza virus infection,¹⁸¹ suggesting that IL-33-ST2 axis may be beneficial for asthma in some situations.

6.4 | Role of TSLP in allergic airway inflammation

TSLP is a distant paralog of IL-7.¹⁸² TSLP transduces its signal through a heterodimeric receptor complex that consists of IL-7 receptor α (IL-7R α) and TSLP receptor (TSLPR), a member of the hemopoietin receptor family most closely related to common cytokine receptor γ chain (γ c).^{182,183} TSLP is expressed in lung- and skin-derived epithelial cells, fibroblasts, endothelial cells, mast cells, macrophages, monocytes, granulocytes, and DCs.¹⁸² Similar to IL-25 and IL-33, the release of TSLP from airway epithelial cells is induced by protease allergens and pro-inflammatory cytokines.¹⁸⁴ TSLP production can also be induced by double-stranded ribonucleic acid (dsRNA) stimulation that mimics viral infections.¹⁸⁵

Polymorphisms of TSLP gene have been shown to be associated with asthma.^{186,187} In addition, the polymorphisms appear to contribute to type 2 immune responses through elevated TSLP production by bronchial epithelial cells in response to dsRNA stimulation.¹⁸⁸ Uller et al.¹⁸⁹ have also demonstrated that airway epithelial cells from patients with asthma respond potently to dsRNA and produce higher levels of TSLP than those from healthy subjects. In addition, Ying et al.¹⁹⁰ have reported that the expression of TSLP mRNA in macrophages is significantly higher in asthmatic patients than that in healthy subjects and that there is a negative correlation between lung function and the expression of TSLP in patients with asthma.

Although several cell types including DCs, Th2 cells, NKT cells, and eosinophils are reported to respond to TSLP, in vivo studies have revealed that DCs and Th2 cells are important for TSLP-mediated allergic responses.¹⁸² Bell et al.¹⁹¹ have shown that TSLP-induced activation of STAT5 in DCs is critical for the development of Th2 cell

responses at barrier surfaces including lung. Moreover, it has been shown that TSLP activates human CD11c⁺ DCs and induces the production of thymus and activation-regulated chemokine (TARC)/CCL17, a Th2 cell-attracting chemokine, and the expansion of CRTH2⁺ memory Th2 cells.^{192,193} Furthermore, it has been reported that TSLP protects ILC2s from steroid-induced cell death,¹⁹⁴ suggesting the possible involvement of TSLP in ILC2-mediated allergic inflammation.

AMG157 is a human anti-TSLP monoclonal antibody that binds human TSLP and prevents interaction with its receptor. In a double blind, placebo-controlled study, the administration of AMG157 reduced allergen-induced bronchoconstriction and airway inflammation during the early and late asthmatic responses in patients with mild allergic asthma.¹⁹⁵ The levels of both blood and sputum eosinophilia after the allergen challenge were also significantly decreased in the AMG157-treated group. The attenuation of allergen-induced bronchoconstriction and airway inflammation by AMG157 indicates a critical role of TSLP in asthmatic responses to environmental allergens.

In summary, among epithelial cell-derived cytokines, IL-33 and IL-25 mainly activate ILC2s, whereas TSLP mainly activates DCs, to induce type 2 immune responses (Figure 1). Recently, Van Dyken et al.¹⁹⁶ have shown that ILC2s and Th2 cells differentiate independently but share overlapping programs which are mediated by exposure to IL-25, IL-33, and TSLP in parasite infection models. Importantly, lack of these three cytokines does not affect priming in lymph nodes, but abrogates the terminal differentiation of effector Th2 cells.¹⁹⁶ However, there is a paucity of information defining the specificity of these cytokines in response to a particular allergen. Further studies are needed to address this point.

7 | ROLE OF ILCs IN ALLERGIC AIRWAY INFLAMMATION

7.1 | Discovery of innate lymphoid cells

In the last decade, the contribution of ILCs to immune responses has become apparent. ILCs can serve as important sources of Th1, Th2, and Th17 cytokines and have been named ILC1s, ILC2s, and ILC3s.^{197,198} ILCs exhibit similar morphologies to T cells/B cells but do not express TCR/BCR or other lineage-specific markers. The development of ILCs and helper T cells has been shown to require the common transcription factors; T-bet for ILC1 and Th1, GATA3 for ILC2 and Th2, and ROR γ for ILC3 and Th17.^{199,200} ROR α is also required for the development of ILC2s.^{201,202}

ILC2s were initially discovered in lymphoid aggregates in the peritoneal cavity called fat-associated lymphoid clusters and named natural helper cells.¹⁶⁹ Natural helper cells express c-kit, Sca-1, IL-7R α , and ST2, and produce large amounts of IL-5 and IL-13 in response to IL-33 or the combination of IL-25 and IL-2.¹⁶⁹ Independently, ILC2s called nuocytes¹⁶⁸ or innate type 2 helper cells (Ih2 cells)²⁰³ were discovered by using IL-13-reporter mice. In humans, ILC2s were found as Lin⁻ cells expressing IL-7R α , CD161, CRTH2, ST2, and transcripts

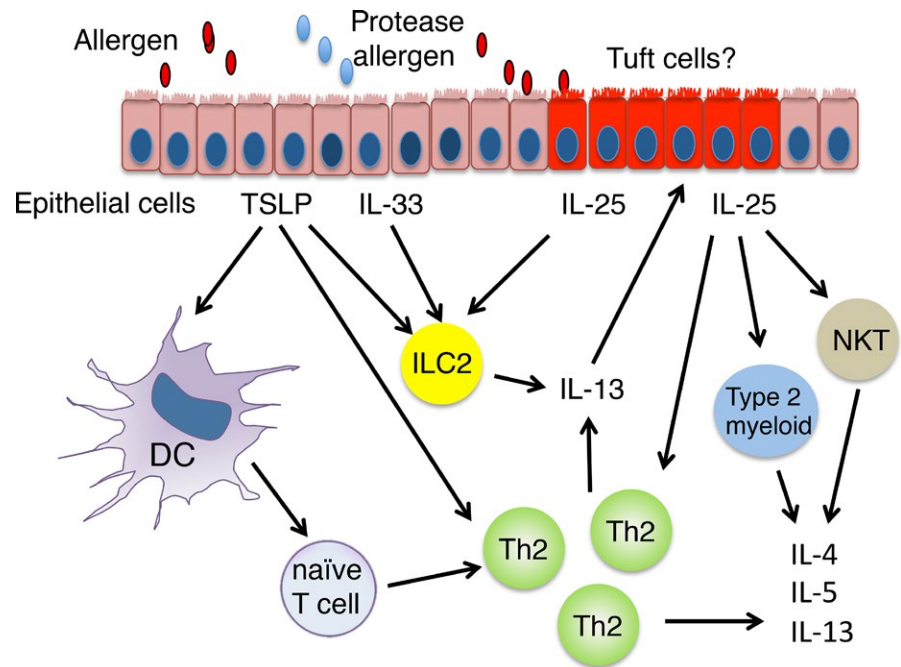


FIGURE 1 A schematic model of crosstalk between epithelial cells and immune cells. Upon allergen stimulation, lung epithelial cells produce TSLP, IL-33, and IL-25, which stimulate ILC2s. TSLP also activates DCs, leading to the development of Th2 cells. In addition, IL-25 activates other immune cells such as type 2 myeloid cells and NKT cells to produce Th2 cytokines, leading to further acceleration of type 2 immune responses. In turn, IL-13, produced by ILC2s and Th2 cells, promotes the differentiation/activation of lung epithelial cells

encoding IL-13.²⁰⁴ ILC2s have been suggested to play a pathogenic role in patients with rhinosinusitis.²⁰⁴ In addition, recent studies have shown that the number of ILC2s is increased in the blood and lung in patients with asthma.^{205,206}

7.2 | Role of ILC2s in asthma

The involvement of ILC2s in asthmatic responses has become evident mostly from mouse studies. Oboki et al.²⁰⁷ have shown that inhalation of protease allergen papain or recombinant IL-33 induces eosinophilic inflammation in Rag2-deficient mice, indicating that innate cells rather than Th2 cells are crucial for eosinophilic inflammation in these models. It has also been shown that administration of IL-25 or IL-33 into the airways leads to the accumulation of ILC2s in the lungs and that ILC2s are the major cellular source of IL-5 and IL-13.²⁰⁸ Moreover, ILC2-derived IL-13 has been shown to play a pivotal role in eosinophilic inflammation and AHR induced by intranasal administration of IL-25.²⁰⁹ In addition, recent studies have shown that lung-resident ILC2s contribute to airway inflammation and AHR induced by protease allergens.^{201,210} These findings suggest that ILC2s play an important role in the development of asthmatic responses at least in some conditions.

ILC2s have also been implicated in response to respiratory viruses. Through IL-13 production, ILC2s contribute to AHR following influenza infection in Rag2^{-/-} mice.¹⁷⁶ However, the depletion of ILC2s in this model leads to impaired lung function and tissue repair, along with increased permeability of the lung epithelial barrier, suggesting that ILC2s are beneficial in this situation. This phenomenon may be explained by the fact that ILC2s can produce amphiregulin,¹⁷⁷ a growth factor linked to tissue remodeling and repair in asthma.²¹¹ It is still unclear whether ILC2s play a role in asthma exacerbation triggered by respiratory viruses in humans.²¹²

7.3 | Crosstalk between ILC2s and T cells

In addition to the roles of ILC2s in the initiation of type 2 immune responses to protease allergens or epithelial cytokines, recent studies have demonstrated that ILC2s can also influence adaptive immune responses. Halim et al.²¹³ have shown that Rorα^{sg/sg} mice which lack ILC2s are impaired in Th2 cell responses to inhaled papain, and that the impaired Th2 cell responses can be reversed by the reconstitution of ILC2s. The impaired Th2 cell responses result from a deficiency in ILC2-derived IL-13, which is critical for efficient induction of Th2 cell responses by inducing the migration of activated DCs to draining lymph nodes where naïve CD4⁺ T cells differentiate into Th2 cells.²¹³ Gold et al.²¹⁴ have also shown that ILC2s are required for the development of allergic airway inflammation induced by multiple intranasal administration of HDM by using chimeric mice that are transplanted with bone marrow of Rorα^{sg/sg} mice. By contrast, in a classical OVA-induced asthma model in which OVA-specific T cells are sensitized by intraperitoneal injection of OVA/alum followed by intranasal OVA challenge, ILC2-deficient mice normally generate Th2 cell-mediated allergic airway inflammation.²¹⁴ Therefore, it is suggested that ILC2s are important for the initiation of Th2 cell differentiation induced by some allergens in the lung but dispensable for inducing allergic inflammation when memory Th2 cells have already been generated by systemic immunization.

Additionally, a recent study has shown that MHC II expression on ILC2s is crucial for the efficient expulsion of parasites from the gut.²¹⁵ Oliphant et al.²¹⁵ have clearly shown that ILC2s process and present antigens, albeit to a lesser extent than cDCs but sufficiently to elicit T-cell proliferation in vitro. In addition, they have shown that crosstalk between ILC2s and CD4⁺ T cells through MHC II-TCR interaction leads to IL-2 production by CD4⁺ T cells and that the produced IL-2 promotes proliferation and IL-13 production of ILC2s.²¹⁵ These findings suggest

a reciprocal interaction between ILC2s and T cells: ILC2s promote Th2 cell differentiation through IL-13 production, while Th2 cells support proliferation and cytokine production of ILC2s by IL-2 production.

7.4 | Role of IL-9 in ILC2-mediated airway inflammation

IL-9 was identified as a cytokine that induces proliferation of T cells and mast cells.²¹⁶ IL-9 is produced by Th2 cells and Th9 cells and utilizes heterodimer of IL-9 receptor (IL-9R) and γc to transduce downstream signaling through JAK/STAT pathways.²¹⁶ Turner et al.²¹⁷ have shown a unique role for IL-9 as an autocrine amplifier of ILC2 function, promoting tissue repair after helminth-induced lung inflammation. It has been shown that ILC2s transiently produce IL-9, along with more sustained IL-5 and IL-13 production, in a papain-induced asthma model and that IL-9 production from ILC2s depends on IL-2 produced by adaptive immune cells.²¹⁸ Although ILC2s are the main source of IL-9 in the papain-induced asthma model,²¹⁸ it remains unclear whether ILC2-derived IL-9 plays a role in allergic inflammation. In this regard, we have recently shown that T-bet are expressed in ILC2s and suppresses IL-9 expression in ILC2s and ILC2-mediated eosinophilic airway inflammation.²¹⁹ We found that while the development of lung ILC2s at steady-state conditions is normal in T-bet^{-/-} mice, IL-33-induced accumulation

of lung ILC2s and eosinophilic airway inflammation are significantly exacerbated in T-bet^{-/-} mice.²¹⁹ Transcriptome analysis revealed that IL-9 expression in IL-33-stimulated lung ILCs is upregulated in T-bet^{-/-} mice as compared with that in wildtype mice.²¹⁹ The neutralization of IL-9 markedly attenuates IL-33-induced accumulation of lung ILC2s and eosinophilic inflammation in T-bet^{-/-} mice.²¹⁹ Taken together, our findings suggest that T-bet suppresses IL-9 production from lung ILC2s and thereby inhibits IL-33-induced eosinophilic airway inflammation. This notion is consistent with a recent finding that ILC2 function is negatively regulated by IFN- γ -STAT1 pathways,²²⁰ which are known to induce T-bet expression in CD4⁺ T cells. The involvement of IL-9 in ILC2 responses is supported by a recent study showing an importance of autocrine loop of IL-9 in survival and cytokine production of ILC2s in response to chitin or migratory helminths.²²¹ It remains unclear whether ILC2-derived IL-9 is similarly involved in the response to airborne allergens such as HDM and fungi.

7.5 | Role of ILC2s in steroid resistance and airway remodeling

Sagani et al.²²² have shown that IL-33 levels are maintained but IL-13 levels are abrogated in endobronchial biopsy specimens from children with severe asthma receiving steroid therapy, suggesting the

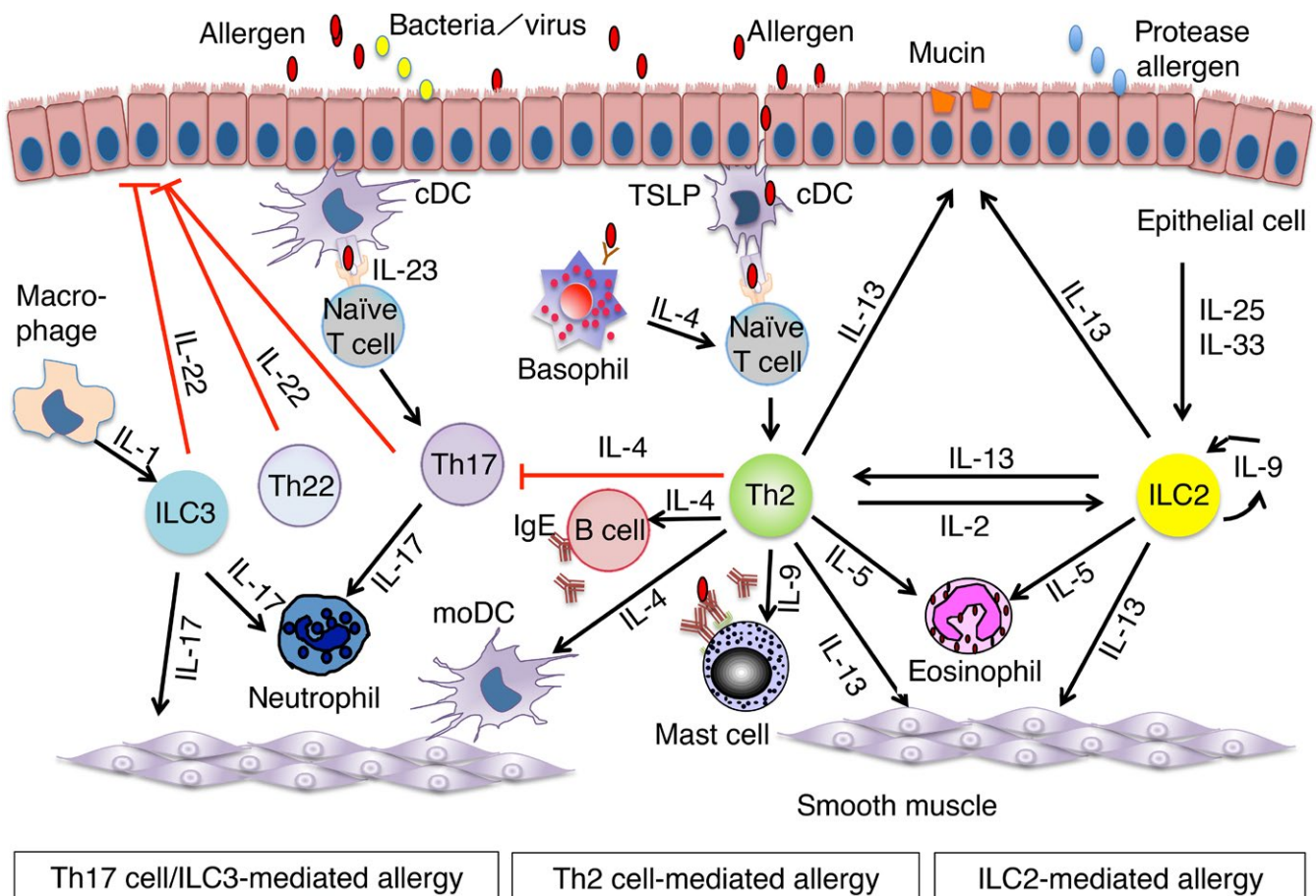


FIGURE 2 A schematic model of allergic airway inflammation. Allergic airway inflammation mainly consists of three pathways: classical Th2 cell-mediated eosinophilic inflammation, ILC2-mediated antigen–non-specific eosinophilic inflammation, and Th17 cell/ILC3-mediated neutrophilic inflammation. There is a complex crosstalk among these pathways

involvement of epithelial cell-derived cytokines-ILC2 axis in the pathogenesis of steroid resistance in asthma. In addition, Kabata et al.¹⁹⁴ have shown that although IL-33-induced inflammatory response can be inhibited by steroid treatment, it becomes steroid-resistant in the presence of allergen exposure. In this situation, ILC2s are more resistant to steroid treatment than Th2 cells.¹⁹⁴ Further investigation indicates that TSLP induced by allergen exposure makes ILC2s resistant to steroid-induced cell death through STAT5 activation.¹⁹⁴ These findings suggest that epithelial cell cytokine-ILC2 axis is involved in steroid resistance in asthma.

Regarding airway remodeling, Saglani et al.²²² have shown a positive correlation between mucosal IL-33 expression and reticular basement membrane thickness in children with severe asthma. As discussed earlier, IL-25 also participates in airway remodeling.^{141,157,158} Relative importance of these epithelial cytokines in steroid resistance and airway remodeling in asthma in humans remains an unsolved question.

7.6 | Role of ILC3s in asthma associated with obesity

Obesity is a major risk factor for the development of asthma, particularly in a severe, steroid-resistant form of asthma.^{223,224} Using murine models, it has been demonstrated that mice fed a high-fat diet spontaneously develop AHR with a significant number of CCR6⁺ ILC3s that produce IL-17A in the lung.²²⁵ ILC3-like cells are also observed in the BALF of patients with asthma.²²⁵ Kim et al.²²⁵ have shown that M1 macrophage-derived IL-1 β plays a critical role in the production of IL-17A from ILC3s in the lung. Therefore, it is plausible that the IL-1 β -ILC3-IL-17A axis participates in the underlying mechanism of asthma associated with obesity. Meanwhile, ILC2s exist constitutively in the visceral adipose tissues and promote the accumulation of eosinophils and M2 macrophages.²²⁶ In this context, both IL-33 and IL-25 have been shown to increase the numbers of ILC2s and maintain a lean phenotype when mice are fed a high-fat diet.²²⁷⁻²²⁹ These studies indicate that ILC2s in the visceral adipose tissue provide protection from fat-associated inflammatory pathology that leads to metabolic syndrome and obesity-associated asthma.

8 | CONCLUSION

Allergic airway inflammation mainly consists of three pathways: classical Th2 cell-mediated eosinophilic inflammation, ILC2-mediated antigen-non-specific eosinophilic inflammation, and Th17 cell/ILC3-mediated neutrophilic inflammation (Figure 2). In addition, Th9 cells and Tfh cells are likely to promote the induction and/or maintenance of allergic airway inflammation, whereas Th22 cells and Treg cells suppress the induction or promote the termination of allergic airway inflammation. Moreover, ILC2-derived IL-13 promotes Th2 cell differentiation, while Th2 cells support proliferation and cytokine production of ILC2s. ILC2s may also be involved in remodeling and repair of damaged tissues in asthma.

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CONFLICTS OF INTERESTS

We have no conflicting financial interests.

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