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Orchestration of Epithelial-derived Cytokines and Innate Immune Cells in Allergic Airway Inflammation

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Abstract

Allergic asthma, a chronic respiratory disease, is a leading worldwide health problem, which inflames and constricts the airways, leading to breathing difficulty. Many studies have focused on the pathogenesis contributed by the adaptive immune system, including CD4⁺ T lymphocytes in delayed type hypersensitivity and B cell-produced IgE in anaphylaxis. More recently, a focus on the airway mucosal barrier and the innate immune system has highlighted, in coordination with T and B cells, to initiate and establish disease. This review highlights the impacts of epithelial-derived cytokines and innate immune cells on allergic airway reactions.

Graphic Abstract

Keywords

Allergic asthma; Epithelial cytokine; Innate lymphoid cell; Invariant natural killer T cell; Granulocyte

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Conflicts of interest

None.

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Introduction

Pathogenic organisms elicit three major cell-mediated immune responses categorized as type 1, 2 and 3 immunity [1, 2]. For instance, intracellular microbes prompt a Type 1 immune response which is characterized by a potent IFN- γ and cytotoxic response by CD4⁺ T helper 1 (TH1) and cytotoxic CD8⁺ T cells, innate cells (such as group 1 innate lymphoid cells (ILC1s) and natural killer (NK) cells), and classically activated (M1) macrophages. Type 1 immune response also involve immunoglobulin G (IgG) antibody production. Type 2 immunity confers protection to helminthes and foreign environmental stimuli such as toxins and venom at both cutaneous and mucosal surfaces by various cells producing interleukin-4 (IL-4), IL-5 and IL-13. These cells include TH2 cells, ILC2s, alternatively activated (M2) macrophages, basophils, eosinophils, mast cells and IgE production. Extracellular bacteria and fungi initiate type 3 immune response characterized by IL-17 and IL-22 producing TH17 cells and ILC3s and by neutrophil activation. Given their protective nature, dysregulation of these responses can lead to autoimmune (type 1 and 3 inflammation) or allergic (type 2 inflammation) diseases. Over the last 50 years, the incidence for autoimmune and allergic diseases has increased in developed countries [3]. Allergic diseases, asthma and helminth infection continue to rise at an epidemic proportion with billions of individuals worldwide suffering and even succumbing to chronic type 2 inflammation. In developing countries, people are in constant exposure to parasitic worms as well as bites and stings from insects and animals that can lead to type 2 inflammation. In developed countries, these exposures are lower but still present; however, industrialization introduces an environmental aspect. This public health problem calls for global action and a deeper understanding of the biological mechanisms regulating type 2 inflammation.

Allergic airway inflammation

Asthma is a chronic lung disease that inflames and constricts the airways, leading to breathing difficulty. Asthma nowadays affects 300 million people worldwide and more than 25 million people (7%) including 7 million children in US (Ref. [4]; CDC data, 2015). Allergic asthma is the most common type of asthma (60% of all cases), which is triggered by inhaled allergens such as pollen, dust mite, pet dander, mold. From an immunological standpoint, allergic airway inflammation describes the sensitization of the epithelium and underlying immune cells to antigenic allergen and subsequent immune response (at the effector phase) as well as tissue repair due to the allergen- and immune-induced damage. Often categorized as a T cell-mediated disease, allergic asthma is associated with TH2 cells and TH2 type cytokines including IL-4, IL-5 and IL-13, which can act on innate immune cells and the mucosal barrier. Among these, IL-5 recruits and activates eosinophils leading to eosinophilia [5]. IL-13 acts directly on airway epithelial cells to induce airway hyper-responsiveness and mucus production [6]. Interestingly, IL-4 induces and maintains TH2 cells, and contributes to IgE class switching in B cells as well as population expansion [7]. Because of the importance of IL-4 in the TH2 responses, one may ask, how is type 2 immunity in allergic airway inflammation initiated? Which type of cells provides the early source of IL-4 or other cytokines (such as IL-13) to drive TH2 differentiation? Are there other upstream mediators that promote and maintain type 2 immune responses in airway

inflammation? The next few sections will discuss and highlight recent work describing the various cells and effectors promoting type 2 immune responses.

Initiation of an allergic microenvironment: allergens, alarmins and PAMPs

Lung epithelial cells (ECs) express a plethora of pattern recognition receptors (PRRs) and act as the first line of defense against pathogens and inhaled allergens. Lung ECs can recognize environmental allergens that drive chronic allergic diseases like asthma [8]. This recognition is through the detection of pathogen-associated molecular patterns (PAMPs). Allergens such as house dust mite (HDM) and HDM fecal pellets contain lipopolysaccharides (LPS) from Gram-negative bacteria that activate toll-like receptors (i.e. TLR4). Several reports have illustrated the amount of LPS (in coordination with an allergen) determines the type of immune response in airway inflammation. Low dose of LPS will allow type 2 immune response to drive airway inflammation while type 1 and 3 occurs with a high dose of LPS [9–11]. Type 2 immune response can occur in the absence of LPS as seen in mice challenged with chitin, a major component of helminthes and insects [12], which is likely through induction of chitinase and activation of protease-activated receptor 2 (PAR-2) [13, 14].

Allergens can also cause direct damage to the lung epithelium. Allergens with protease activity, such as papain and HDM proteases (e.g. Der p1, Der p3, Der p6), disrupt epithelial integrity via tight junction interactions and activate the PAR-2 pathway [15, 16]. Direct cellular damage causes the release of damage-associated molecular patterns (DAMPs). DAMPs, also referred to as alarmins, are host cell-derived molecules released to signal damage/danger to neighboring cells. Alarmins include uric acid, IL-1 α and high-mobility group box 1 protein (HMGB1) recognized by PRRs, cytokine receptors and various other transmembrane receptors.

HDM can cause the release of ATP, uric acid, IL-1 α and HMGB1 by lung ECs [8]. Asthmatic patients have higher levels of HMGB1 compared to healthy patient controls [17]. Various mouse models of allergen-induced airway inflammation have also shown an increase in IL-1 α and HMGB1 and blocking either alarmin ameliorates allergic asthma [18, 19]. Therefore, antigenic molecular pattern recognition or a direct insult to ECs results in the production of various alarmins, cytokines, and chemokines.

The major immune mediators released due to allergen exposure by epithelial cells are IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [20–23]. Interestingly, lung ECs also produces IL-25, IL-33 and TSLP upon exposure to IL-1 α , HMGB1 and uric acid [18, 19, 24]. These alarmins and cytokines are major drivers of type 2 inflammation. These various effector molecules recruit and activate the appropriate immune cells to control and eliminate the allergen/pathogen and initiate epithelial repair. Thus, barrier epithelial cells of the lung sit at the apex of type 2 immunity.

Epithelial cytokines: the early composer of allergic airway inflammation

As described above, lung epithelium can produce type 2 polarizing cytokines IL-25, IL-33 and TSLP [25–27]. These epithelial derived cytokines initiate type 2 responses and can

activate and trigger the production of IL-4, IL-5, IL-9 and IL-13 by innate cells (lymphoid and granulocytes) and TH2 cells (discussed below). Concerning allergic asthma, numerous environmental allergens can trigger the release of IL-25, IL-33 and TSLP. The discovery and inquiry of these epithelial-derived cytokines in response to allergens has brought forth a clearer understanding of the initiation of allergic airway inflammation [8]. Nevertheless, the induction of airway inflammation is a complex process that involves multiple cell types and cytokines. Herein, we discuss the role these epithelial-derived cytokines play in allergic airway inflammation.

IL-25

IL-25, a member of the IL-17 cytokine family, is expressed by a variety of cells besides epithelial cells including T cells, basophils, eosinophils, and mast cells [8]. Nonetheless, bronchial epithelium from asthmatic patients produce high levels of IL-25 and these patients have high plasma levels of IL-25 [28]. Interestingly, IL-25R is highly expressed on eosinophils and basophils in asthmatic patients [29, 30]. IL-25 is critical for airway eosinophilia and can activate and expand ILC2s and TH2 cells [31, 32]. Activation of these cells leads to IL-4, IL-5 and IL-13 cytokine expression. IL-25 also regulates basophil apoptosis, and cytokine expression (IL-4 and IL-13) as well as degranulation [33]. Besides the production of type 2 cytokines on both innate and adaptive immune cells, it also promotes IL-7, IL-33 and TSLP production by stromal cells which further drive airway remodeling and angiogenesis [34].

IL-33

IL-33, one of the newest additions to the IL-1 cytokine family, has been found in numerous inflammatory conditions. Recent genome wide association studies have implicated IL-33 and its receptor ST2/IL1RL1 in various allergic diseases [35, 36]. Allergens papain, HDM, and chitin induce IL-33 [20–23]. IL-33 is mainly expressed in lung epithelial and endothelial cells with a few reports describing hematopoietic cells such natural killer T (NKT) cells, mast cells and macrophages producing IL-33 [37–39]. IL-33 exerts its effects on multiple cells including basophils, eosinophils, mast cells, ILC2s and T cells. Like IL-25, the levels of IL-33 and its receptor ST2 in asthmatic patients are higher than controls and are enhanced upon acute stimulation with an allergen [28], which correlate with asthma severity. In humans, IL-33 expression is elevated in severe allergic disease [40, 41]. Multiple mouse models of allergic diseases have highlighted the role of IL-33 in increased airway hypersensitivity by enhancing IgE production, goblet cell hyperplasia and eosinophilia [42–44]. Blockade of the IL-33/ST2 signals ameliorates murine allergic airway inflammation [45, 46]. IL-33 has also been found to be a potent activator of IL-5 and IL-13 production by ILC2s and IL-4, IL-5 and IL-13 production by basophils [47–49]. IL-33 also enhances the survival and migration of human eosinophils [50].

TSLP

TSLP is an IL-2 cytokine family member utilizing receptor TSLPR and sharing the IL-7 receptor IL-7R α [51, 52]. Similar to IL-25 and IL-33, epithelial cells (lung and skin) are the primary producers of TSLP but it is also produced by basophils, mast cells, macrophages and dendritic cells (DCs) [51, 52]. Numerous cells can respond to TSLP from both innate

(basophils, DCs, eosinophils, ILC2s, mast cells and monocytes) and adaptive (T and B cells) arms of the immune system in addition to airway smooth muscle and epithelial cells [51, 52]. In concert with IL-33, TSLP can induce the production of IL-5 and IL-13 from ILC2s and the differentiation of TH2 cells and the production of cytokines [53, 54]. Additionally, TSLP in coordination with IL-4 can differentiate monocytes into M2 macrophages and alone can lead to basophil activation, expansion and survival [55–57]. Furthermore, stimulation of eosinophils with TSLP results in the degranulation [58]. TSLP also promotes basophil development and activation [56, 59]. Like IL-33, asthmatic patients display genetic polymorphisms in the promoter region of TSLP [60]. TSLP levels are higher in asthmatic patients as well as in animal models of allergic airway inflammation [61, 62]. The blockade of TSLPR in animal models reduces the allergic response demonstrating a potential target for allergic airway inflammation [63, 64].

Taken together, it is likely these epithelial cytokines released upon allergen stimulation act on multiple types of cells to drive allergic inflammatory disease (see details in Table 1).

Innate and innate-like lymphocyte responses to epithelial cytokines

ILC2s

Group 2 innate lymphocytes (ILC2s) were originally found in fat associated lymphoid clusters producing copious amounts of IL-5 and IL-13 when stimulated with upstream type 2 cytokines IL-25, IL-33 and TSLP [65, 66]. ILC2s play an important role in allergic airway inflammation and act as early responders in experimental asthma models [1, 66, 67]. Upon allergen challenge, lung epithelium responds by producing various alarmins and cytokines. Responding to IL-33 (and in concert with other cytokines such as IL-2, IL-4, IL-7, IL-25 and TSLP), ILC2s produce IL-5, IL-9 and IL-13. In addition, ILC2s also produce various amounts of IL-4 dependent of the stimuli [68]. These type 2 cytokines produced by ILC2s feedback on the epithelium, recruit granulocytes and trigger the adaptive immune response [8]. Specifically, IL-5 enhances eosinophil activation and proliferation [69, 70]. A recent study demonstrated that in the bone marrow, ILC2s provide a local source of IL-5 targeting progenitor cells to drive eosinophilia [71]. IL-9 enhances IL-5 and IL-13 production and promotes ILC2 survival and proliferation in an autocrine manner as well as induces mast cell hyperplasia [72, 73]. The production of IL-13 leads to mucus production, smooth muscle contractibility and overall airway hyperreactivity [6]. IL-13 activates mast cells to produce leukotrienes [74]. Leukotrienes, such as LTC₄ can activate ILC2s to produce more IL-5 and IL-13 [75]. IL-13 also induces TGF- β production from eosinophils and mast cells [76], therefore contributing to airway remodeling. Moreover, alternatively activated macrophages contribute to the pathogenesis of inflammatory airway disease due to the abundance of the type 2 cytokine milieu in airway inflammation [77]. Recent reports have shown ILC2s are involved in the recovery phase of inflammation by producing amphiregulin (AREG) to maintain the integrity of the epithelial barrier [78, 79]. In addition to targeting innate cells, ILC2s promote TH2 cell polarization via IL-13-dependent dendritic cell migration to the mediastinal lymph node [80] and MHCII-mediated crosstalk [81, 82]. Mice deficient in ILC2s fail to mount efficient TH2 responses and greatly reduced type 2 inflammation in both lung and gut [81, 83, 84]. TH2 cells, via secretion of IL-2, may also reciprocally

promote ILC2 development [82, 85]. These studies implicate a feed forward circuit between ILC2s and TH2 cells in allergic reactions, thus revealing an essential role of ILC2s in allergic airway inflammation.

iNKT cells

In addition to ILC2s, invariant NKT (iNKT) cells act similarly to ILC2s by responding early and rapidly and are capable of producing type 2 cytokines [86]. iNKT cells are T cells that display invariant TCR α chain that recognizes various forms of glycolipids presented by a MHC class I like molecule, CD1d. Upon antigen stimulation, iNKT cells rapidly produce copious amounts of cytokines including IL-4 and IL-13 [86]. iNKT cells have also been shown to produce type 1 (IFN- γ) and type 3 (IL-17) cytokines as well [86]. iNKT cells have been implicated in the pathogenesis of asthma in human as well as in several mouse models of allergic airway inflammation [87–93]. Although controversy remains about the role of iNKT cells in airway inflammation since IFN- γ production suppresses allergic inflammation, type 2 environmental cues in the airway likely skew iNKT cells towards type 2 cytokine producers. Nevertheless, similar to ILC2s, iNKT cells also respond to IL-25 to produce IL-4 and IL-13 and can respond to IL-33 [94, 95]. iNKT cells may also be a source of IL-33 that promotes IL-5 production by ILC2s and induces eosinophilia [79]. The succession of cytokines produced by these early responders (epithelial cells, ILC2s and iNKT cells) setup a potential pathological condition (via the recruitment of granulocytes) if not properly regulated.

Granulocytic response to epithelial cytokines

Allergens are known to play a significant role in driving allergic airway inflammation by triggering a type 2 response, that in turn, mediates airway inflammatory disorder with IgE responses, tissue eosinophilia, airway remodeling and impaired airway function [5, 66, 67, 96–100]. Granulocyte infiltration is one of the hallmark features of allergic pulmonary disease [5, 66, 67, 96–99]. Recent genome wide association studies have shown that in addition to *IL33* and *IL1RL1*, *GATA2* (3q21), *MHC* (6p21), *HBS1L-MYB* (6q23) and *ERG* (21q22) have been linked to increased basophil and eosinophil counts and with the latter two being directed linked to asthma [101].

High levels of IL-25R on eosinophils in atopic asthmatics reveal the direct effect of IL-25 on granulocytes [28, 29]. In addition to responding to IL-25, an increase in IL-25⁺ eosinophils and basophils has been found in allergen challenged asthmatic patients [28–30]. More recently, IgE stimulation in asthmatic patients increased IL-25R expression on basophils, which was correlated with airway eosinophilia, early onset, and disease severity. Bone marrow-derived mast cells produce IL-25 upon IgE crosslinking; however, it is unclear if the same occurs in allergic airway inflammation [102]. Activation of mast cells leads to prostaglandin D2 (PGD2) and leukotrienes production. ILC2s as well as TH2 cells, which express CRTH2 and CystLTR1, can respond to these inflammatory mediators by producing IL-5 and IL-13 [75, 103–106].

Basophils, eosinophils and mast cells also express the IL-33 receptor, IL-1RL1 [107]. In response to IL-33, basophils produce IL-4, IL-5, IL-9 and IL-13 and demonstrate enhanced

migration towards eotaxin [48, 57, 107]. Although IL-33 does not induce degranulation of basophils, it is greatly enhanced upon IgE crosslinking. Basophils upon activation, promote TH2 cell responses through production of IL-4 and MHCII-mediated interactions, therefore influencing the adaptive arm of allergic responses [108–111]. IL-33 can directly activate human and mouse eosinophils as well as contribute to eosinophil accumulation [40, 50, 107]. Anti-IL-33 treatment in a mouse model of asthma resulted in decreased eosinophilia. The production of IL-5 and IL-13 in response to IL-33 contributes to eosinophilic inflammation. Whereas in mast cells, IL-33 promotes survival, proliferation and the production of type 2 cytokines (IL-4, IL-5 and IL-13) [112].

Similar to IL-3, TSLP promotes basophil growth and differentiation from the bone marrow [59, 113]. Functional heterogeneity has been found in TSLP and IL-3 generated human basophils which correlate with increased airway inflammation susceptibility [113]. Basophils and mast cells themselves can also produce TSLP [114, 115]. Concerning mast cells, TSLP enhances cytokine production [25, 116]. Recently, anti-TSLP and anti-TSLPR antibody showed beneficial effects in patients with mild allergic asthma and in an animal model of allergic airway inflammation, respectively [63, 117].

Summary and Concluding Remarks

Allergic asthma extends far beyond a T cell-mediated disease. It has become evident the innate arm of the immune system involving airway epithelium can initiate a potent type 2 response. This response initiated by IL-25, IL-33 and TSLP working alone or in concert to recruit a combination of inflammatory cells and induce the production of a type 2 cytokines. These inflammatory infiltrates and cytokines drive lung structural cell proliferation and modulate the activity of other cell-types including T and B cells, which contributes to establish chronic inflammation involving IgE-mediated acute type hypersensitivity and T cell-driven delayed type hypersensitivity (the details are outlined in Figure 1). The orchestration of the epithelial-produced cytokines and the innate compartments of the immune system highlights a pivotal role of these factors in initiating disease-associated immune responses at mucosal barrier, including those in asthmatic reactions. Therefore, a deeper understanding of the mucosal barrier responses is required to reach therapeutic resolution in allergic airway inflammation.

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Abbreviations

TSLP	thymic stromal lymphopoietin
TSLPR	TSLP receptor
iNKT	invariant natural killer T cell
TH	CD4 ⁺ T helper cell

ILC2	group 2 innate lymphoid cell
Ig	immunoglobulin
IFN	interferon
IL	interleukin
HMGB1	high-mobility group box 1 protein
PRR	pattern recognition receptors
PAMP	pathogen-associated molecular pattern
DAMP	damage-associated molecular pattern
HDM	house dust mite
LPS	lipopolysaccharides
EC	epithelial cell

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Highlights

- Upon allergen stimulation, airway epithelial cells produce cytokines, IL-25, IL-33, and TSLP
- Epithelial cytokines activate innate lymphoid cells and myeloid cells
- After activation, innate and innate-like lymphoid cells and myeloid cells release effector molecules
- Innate immune cell products impact adaptive immune responses
- Effector molecules from innate and adaptive immune cells act on airway structural cells leading to airway tissue remodeling

Figure 1. Coordination of structural and immune cells and their effector molecules in allergic airway inflammation

When allergens enter the lung tissue from the airway acting on the epithelial cells, the airway epithelium responds by releasing cytokines, IL-33, IL-25 and TSLP. ILC2s, basophils, eosinophils and mast cells can respond to all three cytokines resulting in the production of effector cytokines (IL-4, IL-5 and IL-13) from these early innate responders. ILC2s also can produce AREG to initiate epithelia repair. Allergens can be taken up by dendritic cells (DCs) residing in the lung tissue. IL-13 production by ILC2s and other innate cells such as basophils primes DCs and promotes their migration into lung draining mediastinal lymph nodes, where the primed DCs present allergen-loaded MHCII complex to polarize naïve progenitor CD4⁺ T helper cells into TH2 cells. Differentiated TH2 cells migrate into the lung tissue and secrete IL-4, IL-5 and IL-13, resulting in eosinophilia and severe airway inflammation. Another important role of TH2 cells is that they provide IL-4 and IL-13 to germinal center B cells that undergo antibody class switching to secrete allergen-specific IgE that arms basophils and mast cells. Together, the innate players and the adaptive compartments contribute to allergic airway inflammation, and epithelial and smooth muscle cell hypertrophy.

Table 1

Effects of epithelial cell cytokines in allergic airway reactions.

Initial Cytokine	Targeted Cell Types	Induction of Downstream Effector Molecules or Events	References
IL-25	ILC2	<ul style="list-style-type: none"> IL-5, IL-9, IL-13 	[8, 47, 53, 65, 66, 104]
	T Cell	<ul style="list-style-type: none"> IL-4, IL-5, IL-13 (TH2) IL-4, IL-13 (iNKT) 	[8, 94, 95, 118]
	Eosinophil	<ul style="list-style-type: none"> Induce eosinophilia 	[118]
	Basophil	<ul style="list-style-type: none"> Inhibit Apoptosis Enhance IgE-mediated degranulation 	[8]
IL-33	ILC2	<ul style="list-style-type: none"> IL-4, IL-5, IL-9, IL-13, GM-CSF, AREG Promote expansion and migration 	[8, 47–49, 53, 65, 66, 68, 78, 104, 119]
	T Cell	<ul style="list-style-type: none"> IL-4, IL-5, IL-13, IFN-γ, TNF-α (CD4⁺ TH) IL-4, IL-5, IL-13, IFN-γ, TNF-α, IL-2 (iNKT) IFN-γ, TNF-α (CD8⁺) 	[48, 94, 95, 107]
	Eosinophil	<ul style="list-style-type: none"> IL-4, IL-5, IL-6, IL-13, TGF-β, CCL17 Induce eosinophilia Enhance survival and adhesiveness 	[8, 40, 42–44, 50, 107, 120]
	Basophil	<ul style="list-style-type: none"> IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF, LTC₄, Histamine 	[47–49, 57, 107, 120]
	Mast Cell	<ul style="list-style-type: none"> IL-4, IL-5, IL-13, IL-6, TNF-α, GM-CSF, MIP-2, KC, MIP-1α, MCP-1, MCP-3, CCL4, CXCL8, Histamine, Leukotriene, PGD2 (controversial) Enhance survival and proliferation 	[107, 112, 121–124]
TSLP	ILC2	<ul style="list-style-type: none"> IL-5, IL-13, IL-9 	[53, 65, 66, 119]
	Cell	<ul style="list-style-type: none"> IL-4, IL-5, IL-13 (TH2) 	[51, 54]
	Eosinophil	<ul style="list-style-type: none"> IL-5, IL-13, IL-6, TNF-α, CCL2, CCL3, CCL4, CXCL8, CXCL1 	[125, 126]
	Basophil	<ul style="list-style-type: none"> IL-3, IL-4, IL-5, IL-13 	[56]
	Mast Cell	<ul style="list-style-type: none"> IL-5, IL-13, IL-10, IL-6, GM-CSF, TNF-α, IL-1β, CCL1, CCL4, CCL5, CCL11, CCL22, CXCL10, CXCL8, PGD2 	[25, 116, 127]
	Dendritic Cell	<ul style="list-style-type: none"> CCL17, CCL22, CXCL8, IL-15 	[128]
	Macrophage	<ul style="list-style-type: none"> CCL-2, CCL-13, CCL17, CCL22, CCL24 	[55]