DYNAMIC ROLE OF EPITHELIAL-DERIVED CYTOKINES IN ASTHMA

Kathleen R. Bartemes, B.A. and **Hirohito Kita, M.D.**
Division of Allergic Diseases, Department of Internal Medicine, and Department of Immunology, Mayo Clinic, Rochester, MN 55905

Abstract

Asthma is an inflammatory disorder of the airways, characterized by infiltration of mast cells, eosinophils, and Th2-type CD4+ T cells in the airway wall. Airway epithelium constitutes the first line of interaction with our atmospheric environment. The protective barrier function of the airway epithelium is likely impaired in asthma. Furthermore, recent studies suggest critical immunogenic and immunomodulatory functions of airway epithelium. In particular, a triad of cytokines, including IL-25, IL-33 and TSLP, is produced and released by airway epithelial cells in response to various environmental and microbial stimuli or by cellular damage. These cytokines induce and promote Th2-type airway inflammation and cause remodeling and pathological changes in the airway walls, suggesting their pivotal roles in the pathophysiology of asthma. Thus, the airway epithelium can no longer be regarded as a mere structural barrier, but must be considered an active player in pathogenesis of asthma and other allergic disorders.

Keywords

asthma; epithelium; IL-25; IL-33; TSLP

1. Introduction

Asthma is a syndrome, which is characterized by chronic inflammation of conducting airways, remodeling of airway walls, airway hyperresponsiveness (AHR) to non-specific stimuli, and episodic exacerbations of airway obstruction. Infiltration of mast cells, eosinophils, type 2 CD4+ T cells (Th2 cells) and Th17 cells in the airway walls is observed in patients with asthma, even those with mild severity or without symptoms. Because airway challenge of sensitized patients or experimental animals that are immunized with antigens induces Th2-type inflammation [1], it has been considered that Th2-type immune responses to allergens play a major role in the pathogenesis of asthma. However, not all asthma involves allergic sensitization or presence of serum IgE antibodies. The patients with non-allergic (called intrinsic) asthma share most of the pathologies and, indeed, Th2-type airway inflammation as those patients with IgE antibodies (called extrinsic). Considerable evidence exists that Th2 cells are responsible for many of the features of asthma. For example, Th2 cells and Th2-type cytokines are detected in bronchoalveolar-lavage (BAL) fluids or lung

Corresponding author: Hirohito Kita, MD, Department of Immunology, 200 First Street SW, Rochester, MN 55905, Telephone; 507-284-6109, Fax; 507-284-5045, kita.hirohito@mayo.edu.

tissues from patients with asthma [1]. Treatment of patients with asthma by targeting Th2 cytokines can be effective, especially in patients with severe and refractory asthma [2]. In addition, IL-17 expression is also observed in patients with asthma, and the severity of AHR correlates with IL-17 expression levels [3, 4]. A novel subset of memory "Th2 cells" that produces IL-17 and exacerbates airway inflammation has also been identified [5]. This evidence suggests the importance of Th2- and perhaps Th17-type T cells in driving airway inflammation and pathological changes in asthma; however, our knowledge is limited concerning how asthma patients develop such dysregulated Th2 and Th17 immune responses in their airways.

Our understanding of the pathogenesis of asthma has undergone great transformation throughout the years. We have moved from an understanding of asthma as a disease primarily of airway caliber to the concept of dysregulation of airway immunity that drives chronic inflammation and structural anomalies. More recently, the immune response in asthmatic airways is considered a result of aberrant functions of the airway epithelium [6]. That is, damage to the airway epithelium or dysregulated activation of airway epithelium by exposure to atmospheric insults, allergens, and viruses and bacteria may play central roles in driving Th2-type immune response and chronic airway inflammation. In this regard, there has been particular interest in new cytokines, including thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. These cytokines are produced by airway epithelial cells as well as other immune and structural cells and are uniformly implicated in Th2-type immune responses. Several genetic studies found strong associations with risk of developing asthma and single nucleotide polymorphisms (SNPs) in genes for these cytokines and their receptors, including *IL1RL1/IL18R1*, *TSLP* and *IL33* [7–9]. Therefore, the focus of this review is to highlight recent advances in our understanding of the biology and the roles of these epithelial cell-derived cytokines, TSLP, IL-25 and IL-33, in the airway immune response and discuss how abnormalities of airway epithelial functions may impact airway inflammation, airway structure, and inception and progression of asthma.

2. Functions of airway epithelium

The epithelial cell layer that is lining the airway wall provides the first line of protection against environmental pathogens by several mechanisms. Structurally, it acts as a physical barrier, excluding potential invaders from the underlying tissues [10]. It also secretes a number of anti-microbial peptides, such as defensins, cathelicidins and collectins, and reactive oxygen species (ROS), which are directly toxic to pathogens [11]. Anti-microbial peptides also recruit and activate inflammatory cells, such as neutrophils [10, 11]. Airway epithelium also acts as an immunological barrier. Airway epithelial cells recruit and activate immune cells by releasing cytokines and chemokines, such as IL-6, IL-8, eotaxins, and GM-CSF [11]. Indeed, airway epithelial cells are poised to respond rapidly to the microbial organisms and environmental molecules in the airway lumen, due both to proximity to the external environment and by expression of the receptors for them. For example, protease-activated receptors (PARs) on epithelial cells can be triggered by a subset of environmental allergens that contain proteolytic activity, such as fungi, house dust mites, and cockroaches. Likewise, lipolysaccharide (LPS) and other microbial components can activate Toll-like receptors (TLRs), prompting epithelial cells to release inflammatory mediators [12]. Among these mediators, there has been considerable interest in novel epithelial cell-derived cytokines, including IL-25, IL-33 and TSLP. Indeed, upon activation through PARs and TLRs, epithelial cells produce and release these cytokines [13]. Furthermore, IL-33 is released upon damage to the epithelium, such as mechanical injury [14, 15] or UVB light treatment [16], and is considered an "alarmin" that provides a link between tissue damage/injury and immune responses. Thus, airway epithelial cells are no longer considered a mere

barrier and may play a pivotal role in regulating the immune responses and inflammation in airway mucosa.

3. Epithelial-derived cytokines that regulate Th2 immunity

IL-25, IL-33 and TSLP are all implicated in promoting Th2-type immune responses. However, these cytokines are quite dissimilar and belong to different cytokine families. To understand better how these cytokines are involved in Th2-type immune responses, it is important to understand the cellular sources as well as biological responses to these cytokines. The information is summarized in Table 1. This section serves to highlight the key characteristics of these cytokines.

3.1. IL-25

IL-25 is a member of the IL-17 family. Most of Th17-family members are known to promote neutrophilic inflammation. In contrast, IL-17E, also known as IL-25, does not appear to play a role in neutrophilic responses, but rather is known to promote Th2 responses or eosinophilic inflammation [17, 18]. Indeed, IL-25 may serve as a counter regulator for other IL-17 family members. Increased levels of IL-25 inhibit Th17 development and blockade of IL-25 enhances IL-17 production [19, 20]. IL-25 signals through a heterodimeric complex of IL-17RA and IL-17RB [21] and induces TRAF6-mediated activation of NF-κB [22]. It also has been shown to activate NFATc1 and JunB [17].

IL-25 can be produced not only by epithelial cells, but also by Th2 cells, mast cells, macrophages, eosinophils and basophils [17, 18, 23–26]. The IL-25 receptor, IL-17RB, is expressed on basophils [27], NKT cells, and recently identified type 2 innate lymphoid cells ([28], and more details below); no IL-17RB has been identified on CD4+ T cells.

3.2. IL-33

IL-33 is a member of the IL-1 cytokine family, which includes IL-1β and IL-18. IL-33 was originally discovered as a nuclear factor of high endothelial venules (NF-HEV), [29] and is constitutively expressed by some tissue structural cells, including epithelial cells. Each of the IL-1 family members likely drives different immune responses. IL-33 is implicated in Th2-type immunity, and IL-1β and IL-18 are associated with Th17- and Th1-type immune responses, respectively [30]. The IL-33 receptor is dimeric, consisting of an IL-1R-like subunit (IL-1RL1, also known as ST2) that associates with the IL-1R accessory protein (IL-1RAcP). Similarly to other IL-1 family cytokines, IL-33 signals through MyD88, IRAK, JNK, p38, p44/42, JAK2 [31] and activates NF-kB. Importantly, ST2 was first identified as a marker of Th2 cells even before its ligand was identified [32, 33].

While IL-33 belongs to the IL-1 family, the regulatory mechanisms for production and release of IL-33 are distinct from those for IL-1β and IL-18. IL-33 is constitutively expressed and stored as a 30 kDa full-length precursor form. Proteolytic cleavage of the proforms of IL-1β and IL-18 by caspase-1 activates these cytokines and allows them to be secreted extracellularly. In contrast, full-length IL-33 has immunological activities and cleavage of IL-33 by caspase-1 inactivates the cytokine [34–36]. Therefore, it has been proposed that full-length IL-33 is released from nuclei of the cells by cellular injury or necrosis and triggers immune responses [37]; cellular apoptosis that initiates caspase cleavage of IL-33 may inactivate the protein and prevent unnecessary immune responses. Nonetheless, overexpression of full-length IL-33 recently resulted in secretion of a biologically active 18 kDa cleaved product that mimics the pathologies of IL-33-mediated inflammation [38]. A splice variant of IL-33 that lacks the proposed caspase-1 cleavage site activated a human mast cell line (HMC-1) and a mouse macrophage line (Raw 26.7) in an

ST2-dependent manner [35]. Therefore, more studies are necessary to elucidate the structure and functional relationships of IL-33 and the mechanisms involved in production and extracellular release of "active" IL-33 during immune responses in vivo.

Besides epithelial cells [39], IL-33 is produced by other structural cells, such as endothelial cells, bronchial smooth muscle cells, fibroblasts, keratinocytes and adipocytes [39–41]. Immune cells, such as dendritic cells (DCs), macrophages, and mast cells may also produce IL-33 [39, 42]. IL-33 receptor, ST2, is expressed on a wide variety of cell types, including vascular endothelial cells, epithelial cells, eosinophils, mast cells, B cells, basophils, NK, NKT, and fully differentiated Th2 cells [43–49], implicating the potential roles of IL-33 in asthma as well as many other inflammatory disorders. In addition, novel innate lymphoid cells that produce large quantities of Th2-type cytokines in response to IL-25 or IL-33 have been identified recently in gastrointestinal organs [50–53]. Specifically, intraperitoneal injection of IL-25 or IL-33 into mice led to the expansion of cells that produce IL-4 and/or IL-13 in gut-associated lymphoid tissue (GALT) [53] and in mesenteric lymph nodes (LNs) and spleen [51]. Likewise, an IL-33-responsive cell type with a lymphoid morphology was identified in fat-associated lymphoid clusters (FALCs) in the mesentery layer [50]. These innate lymphoid cells lack conventional lineage markers but often express IL-7Ra, Sca-1, c-Kit, CD44, CD25, Thy1.2, and ICOS. Importantly, similar innate lymphoid cells have also been identified in the lungs and bone marrow of naïve mice and those mice infected with virus or exposed to allergens [54–58], suggesting roles for these innate cells in Th2-type airway inflammation and asthma.

3.3. TSLP

TSLP is a type I four α-helical bundle short-chain cytokine and is part of the IL-2 family [59, 60]. It signals through a heterodimeric receptor complex consisting of the IL-7Ra chain and a γ_c –like chain specific for TSLP (TSLPR) [61]. Signaling occurs through Stat5 phosphorylation [62]. However, requirements for JAK, specifically JAK1 and JAK2, are controversial [62, 63]. The primary source for TSLP is epithelial cells, but basophils, mast cells and keratinocytes have also been shown to produce TSLP [64–69]. TSLPR is found on DCs, mast cells, monocytes, macrophages, B cells, T cells, basophils and eosinophils [60, 69, 70] as well as on epithelial cells themselves [71].

4. Roles of IL-25, IL-33 and TSLP in Th2-type airway inflammation and asthma

The roles for IL-25, IL-33 and TSLP in Th2-type airway inflammation have been studied in a variety of mouse models, including systemic and airway administration of these cytokines, systemic or topical expression of cytokine genes, and Th2-type immune responses models with allergens, model antigens [e.g. ovalbumin (OVA)], and helminthes infection. These studies consistently find potent activities of these cytokines to mediate Th2 type immune responses. For example, transgenic overexpression of IL-25 [18, 72–74] induces Th2 cytokine expression in tissues, airway eosinophilia, increased serum levels of IgE antibodies and Th2 cytokines, mucus overproduction, goblet cell hyperplasia, airway wall thickening, and AHR; these inflammatory and pathological changes are consistent with human asthma. Similarly, systemic administration of exogenous IL-25 induces AHR, inflammation and mucus overproduction, which are dependent on IL-13, IL-4Ra or STAT6 [75]. Interestingly, IL-25-induced airway pathological changes are apparent in mice deficient in Rag1 gene, suggesting that innate immunity, rather than T cells or B cells, mediates the responses [18, 76]. Furthermore, a novel subset of natural killer T (NKT) cells that expresses the IL-17RB and predominantly produces IL-13 and chemokines upon stimulation with IL-25 was implicated in AHR induced by airway administration of lipid antigens [77]. In an OVA-

induced Th2-type airway inflammation model, mice injected with soluble IL-17RB protein or anti-IL-25 antibody or those deficient in the IL-25 gene showed reduced production of IgE antibody and were protected from development of Th2-type airway inflammation [78–81]. These findings suggest that IL-25 is involved in Th2-type airway inflammation through both innate and adaptive immunity.

Similar biological activities are observed with IL-33. When IL-33 is administered systemically, mice develop airway eosinophilia as well as increased production of Th2-type cytokines and mucus in the lungs [39]; again, these pathological changes are retained in Rag2-deficient mice [47]. Indeed, airway administration of IL-33 induced marked increases in eosinophil number and IL-5 and IL-13 levels in the airways, which are mediated by novel type 2 innate lymphoid cells as described earlier [55]. Furthermore, in vivo airway administration of ubiquitous allergens, such as *Alternaria alternata*, induced hallmark features of Th2-type airway inflammation that is dependent on IL-33 and the novel type 2 innate lymphoid cells [55]. These findings suggest that airway inflammation induced by IL-33 is at least in part mediated by innate immunity, in particular the novel lymphoid cells. In addition, lack of the ST2 (i.e. IL-33 receptor) gene or administration of anti-ST2 Ab or ST2 fusion protein attenuated production of Th2 cytokines and eosinophil infiltration in various mouse models of airway inflammation [32, 82–84]; these studies used adoptive transfer of differentiated Th2 cells or helminthes or fungal infection models. On the other hand, in IL-33-deficient mice that were sensitized and challenged with OVA antigen, IL-33 was necessary for airway eosinophilia and AHR but not for production of IgE antibodies and Th2 cytokines, suggesting that IL-33 may be involved only in the early and innate Th2 response but may not be necessary for subsequent adaptive immune responses [85]. Similarly, in the OVA model, airway eosinophilia and Th2 cytokines were not affected or attenuated only during a narrow window of time in ST2-deficient mice [86, 87]. Altogether, IL-33 clearly mediates Th2-type airway inflammation by activating innate immune cells, but the contribution of IL-33 in antigen-specific Th2-type immunity may be dependent on the model.

Transgenic overexpression of TSLP in the airway also induces asthma-like pathologic changes in mice, consisting of airway eosinophilia, increases in serum IgE and BAL Th2-type cytokines, AHR, increased mucus production, and thickening of airway epithelium [88]. However, unlike IL-25 and IL-33, the ability of TSLP to induce innate Th2-type immunity may be limited. For example, overexpression of TSLP alone in the airways caused a weak innate response and was insufficient for development of robust airway inflammation [89]. Both overexpression of TSLP and airway administration of OVA antigen were required to induce disease development [89], suggesting that TSLP induces predisposition toward the development of aberrant responses against innocuous environmental antigens. Other evidence also suggests a role for TSLP as a link between innate and adaptive Th2-type immune responses. Airway eosinophilia and airway remodeling in an OVA-induced allergic airway inflammation model were attenuated in mice lacking the TSLPR [88, 90]. TSLP primes antigen-presenting cells, such as DCs, as treatment of mice with anti-TSLPR or soluble TSLPR prior to OVA sensitization inhibited DC maturation (expression of CD40, CD80, CD86, MHC II), decreased the number of OVA-bearing DCs in the draining lymph nodes and prevented Th2-type sensitization to the antigen [91, 92]. TSLP may also directly act on CD4+ T cells. Allergic airway inflammation was restored in TSLPR KO mice when they were reconstituted with wild-type CD4+ T cells [62, 90, 93]. TSLP inhibited development of induced regulatory T cells (iTregs) from naïve CD4+ T-cells [94], suggesting that TSLP may break immunological tolerance. Likewise, mice sensitized with OVA plus TSLP had fewer OVA-specific iTregs in the draining lymph nodes than did mice sensitized with OVA alone [94]. Altogether these findings suggest that TSLP plays pivotal roles in Th2-type immune responses and asthma-like airway inflammation likely through

mechanisms involving the interface between the innate and adaptive immunity and/or adaptive immunity itself.

5. Effects of IL-25, IL-33 and TSLP on airway epithelium

While IL-25, IL-33 and TSLP are produced by airway epithelial cells, these cytokines affect the functions and integrity of airway epithelium itself either directly or indirectly through activation of airway immune cells. Thus, these cytokines may create a feedback loop between airway epithelial cells and immune cells in respiratory mucosa, which is likely important in the pathophysiology of asthma. Sections 5.1 – 5.3 will highlight current concepts and new discoveries about how these feedback loops drive and sustain Th2-type immunity and pathology in the airways.

5.1. Barrier function

In asthma, impaired epithelial barrier function may render the airways vulnerable to infection or colonization with microorganisms and increase epithelial permeability to environmental molecules, resulting in priming of DCs and development and/or exacerbation of Th2-type immune responses [6]. Physical damage to the epithelial cells as well as markers of stress and injury are observed in patients with asthma. Epithelial barrier function is provided by the structure of the epithelial cells and by the tight junctions between epithelial cells. Furthermore, Goblet cells and Clara cells secrete mucins and surfactants, respectively, that provide a surface coating that is able to both trap and carry away inhaled particles. Epithelial cells from patients with asthma are less efficient in formation of tight junctions than cells from normal individuals [95, 96]. The tight junction formation of airway epithelial cells is further reduced by exposure to environmental insults, such as tobacco smoke [96]. When skin barrier function is disrupted by a mutation of Notch in mice, the levels of skin tissue TSLP are increased [97]. Exposure of airway epithelium to a cysteine protease, papain, induces ROS generation by DCs and epithelial cells, resulting in oxidized phospholipids that stimulate epithelial cells to release TSLP through the TLR4-TRIF pathway [98]. These finding suggest that defective barrier or increased inflammatory mediators trigger epithelial cells to produce TSLP and potentially other cytokines, resulting priming of the mucosal tissue to develop Th2-type immunity.

5.2. Epithelial remodeling

Thickening of the basement membrane and airway walls and altered mucus production by epithelial cells are all hallmarks of chronic asthma and lead to narrowing of the airways. Mucin, produced in excess by epithelial cells (i.e. goblet cell metaplasia), combined with DNA and eosinophil proteins, creates viscous mucus that can plug the airways. These are several pieces of evidence to suggest that IL-33 and TSLP are involved in these epithelial remodeling and pathologic changes. Thickening of the basal lamina, part of the basement membrane, can be induced by subjecting the epithelium to chronic injury or stress, to infection and inflammation, and to profibrotic cytokines, such as IL-13, VEGF, and TGF-β. IL-33 may play a role in basement membrane thickening by inducing IL-13 and TGF-β production by infiltrating eosinophils [99]. Furthermore, gut epithelial cells in response to pathogens produce TSLP; this initial TSLP drives IL-13 production by immune cells and IL-13 then further enhances TSLP expression [100], suggesting a positive feedback between TSLP and IL-13 in epithelium. IL-33 also enhances substance P-induced release of VEGF by mast cells [101, 102]. In a mouse model of chronic airway inflammation, anti-ST2 when combined with CpG attenuated mucus cell metaplasia [83], suggesting potential therapeutic benefit of blocking the IL-33 pathway.

The pathological changes in asthma also involve the airway walls, smooth muscle tissues (ASM) and vascular structure. These tissue cells can be directly activated by epithelial cell-derived cytokines or indirectly by the cytokines (e.g. IL-13) that are produced by immune cells in response to these cytokines. For example, fibroblasts in the airway walls may contribute to remodeling by secreting matrix proteins, such as collagens and fibronectins, in response to IL-13 or TGF-β mediated by IL-25, IL-33 or TSLP. IL-25 directly induces VEGF and VEGFR expression by vascular endothelial cells [101]. Subcutaneous administration of IL-33 induces cutaneous fibrosis in a mechanism that appears to involve the release of IL-13 by IL-33-stimulated eosinophils [103]; anti-IL-5 treatment and subsequent reduction of eosinophils numbers in airway mucosa markedly reduced deposition of collagen and other matrix proteins in human asthma [104, 105]. In atopic dermatitis, TSLP causes fibroblasts to produce collagen [106]. Similarly, IL-33 drives maturation of mast cells precursors [107], and mast cell-derived mediators may act on airway smooth muscle cells to induce airway pathology including remodeling [108].

5.3. Viral-induced airway epithelial changes

Early viral infections, in particular respiratory viral infections in children, have been linked to subsequent development of asthma. In addition, at least half of all asthma exacerbations in adults and children are the result of upper respiratory tract infections. Convincing evidence suggests that viral infection, viral ssRNA and viral dsRNA induce IL-25, TSLP, and IL-33 release by epithelial cells in vitro [109–112]. These viral-mediated epithelial cytokines may contribute to Th2-type airway inflammation in the airways in vivo. For example, infection of mice with influenza virus induces IL-33 release from alveolar macrophages, resulting in production of IL-13 by type 2 innate lymphoid cells and induction of AHR [57]. A recent series of studies by Siegle et al have attempted to utilize airway epithelial changes in response to viral infection to create a "natural" model for inducing chronic asthma in mice. Mice subjected to frequent inhalation exposure to low levels of aerosolized OVA developed tolerance to OVA. In contrast, if the mice were first infected with pneumonia virus of mice (PVM), mice developed features of chronic asthma and subsequent challenge with OVA elicited asthma-like exacerabations [113]. Moreover, PVM infection enhanced airway IL-25 production, and antibody blockade of IL-25 prior to antigen sensitization attenuated airway remodeling and eosinophilia [113], suggesting a critical role for IL-25 in priming the airways to antigen sensitization in this model. Furthermore, IL-33-induced lung inflammation is inhibited by the presence of iNKT cells through their production of IFN-γ [114]. Severe RSV infection in infants reduces the number of circulating NK cells, and is correlated with increased incidence of asthma later in life [115]. Therefore, respiratory viral infection in particular early in life may mediate Th2-type immunity in the airways by several mechanisms by modulating the IL-25 and IL-33 pathways.

While production of IL-25 and IL-33 by airway epithelium in response to viral infection may be detrimental to the host by promoting Th2-type immune responses, these cytokines can also be protective against extensive lung damage and may facilitate the healing process in certain settings. For example, IL-25- and IL-33-responsive innate type 2 immune cells accumulated in the lungs after infection with influenza virus [116]. Depletion of these innate lymphoid cells resulted in loss of airway epithelial integrity, diminished lung function and impaired airway remodeling; these defects were restored by administration of amphiregulin, a product of innate lymphoid cells. These results suggest roles for Th2-type innate lymphoid cells in restoring airway epithelial integrity and tissue homeostasis after infection with influenza virus. Thus, epithelial cell-derived cytokines may be a "two-edged sword" during airway infection with respiratory viruses.

6. Links to human asthma

There is accumulating evidence available to suggest that the IL-25, IL-33 and TSLP pathways are associated with human asthma. For example, patients with asthma demonstrate increased IL-25 and IL-17RB mRNA transcription in their lung biopsy specimens [26]; IL-25+ cells are evident in the submucosal tissues [117]. When patients are challenged with inhaled allergens, the number of IL-25+ and IL-25R+ cells in bronchial biopsies increases, and the increase in IL-25 expression correlates with severity of bronchial constriction [118]. In addition, basophils from patients with seasonal allergic rhinitis show increased surface IL-17RB after allergen challenge [27]. Similarly, serum from asthmatic patients contains increased levels of soluble ST2 as compared to control individuals and those levels are enhanced during asthma exacerbation [119]. In patients with chronic rhinosinusitis, airway epithelial cells from patients who are resistant to treatment expressed increased levels of IL-33 mRNA [120] as compared to those responsive to treatments. IL-33 was increased in epithelial cells from bronchial biopsies and in BAL fluids from patients with moderate to severe asthma as compared to normal controls [121]. Expression of IL-33 by airway epithelial cells is also increased in patients with allergic rhinitis [122].

A strong connection between TSLP and human allergic diseases was originally made with patients with atopic dermatitis [67]. TSLP was also overexpressed in the skin of individuals with Netherton syndrome, a severe skin disease characterized by atopic dermatitis-like lesions that result from mutations in the serine peptidase inhibitor Kazal-type 5 (SPINK5) gene [64]. Likewise, increased evidence is available regarding the roles for TSLP in human asthma. Epithelial cells from asthmatic subjects constitutively express more TSLP than do healthy subjects [71], and the levels of TSLP in the airways of asthmatic individuals are correlated with disease severity [123, 124]. Bronchial epithelial cells from individuals with asthma release more TSLP upon exposure to dsDNA than do those from healthy controls [125]. Human airway epithelial cells produce TSLP in response to environmental factors, such as fungal proteases and respiratory viruses [110, 112, 126] and the response is significantly enhanced in the presence of inflammatory cytokines, such IL-4, IL-13, IL-25, TNFα, TGFβ, and IFNβ [110, 127].

Genetics links have been made between asthma and allergic diseases and polymorphisms in the genes encoding IL-25, IL-33 and TSLP and their receptors. For example, polymorphisms in the *IL33* gene are associated with Japanese patients with allergic rhinitis [128]. SNPs in the distal promoter of the *IL1RL1* (or *ST2*) gene are associated with atopic dermatitis and children with asthma presenting acute symptoms [129, 130]. Genetic studies also support a critical role for TSLP in asthma. Several SNPs at the TSLP genomic locus were associated with increased asthma susceptibility or protection in multiple ethnic backgrounds [131–133]. One such SNP present in the genomic TSLP locus creates a novel AP-1 transcription factor binding site that could potentially lead to increased TSLP transcription [131]. SNPs at *IL17RB* (i.e. IL-25 receptor gene) also have been associated with asthma [134]. Importantly, *IL33*, *IL1RL1* (i.e. ST2) and *TSLP* genes have been implicated in asthma in recent large-scale genome-wide association scan studies [8, 9].

7. Conclusion and future directions

Current evidence suggests potent activities of IL-25, IL-33, and TSLP in promoting Th2-type immune responses by affecting various cell types involved in innate and adaptive immune responses such as DCs, CD4+ T cells, innate type 2 lymphoid cells and NKT cells (Figure 1). Th2-type cytokines produced by these immune cells may induce eosinophilic inflammation of the airways and cause structural changes in airway epithelium and other tissue components, consistent with the pathology of asthma. Human clinical studies and

genetic studies also suggest dysregulation of the IL-25, IL-33 and TSLP pathways in patients with asthma. Thus, by producing these cytokines, airway epithelium may play central roles in pathophysiology of asthma and allergic disease. In addition, the roles for TSLP and IL-25 in inhibiting iTreg functions underscore the importance of airway epithelium in breaking tolerance in asthma as well as a variety of other human diseases [94, 135–138]. Furthermore, epithelial cell-derived cytokines, which are released in response to environmental allergens or microbes, may act to augment continued activation of airway epithelial cells themselves in an autrocrine fashion [139–141]. Such self-perpetuating mechanisms mediated by cytokines in the airway epithelium may explain the chronic and persistent inflammation that is observed in patients with asthma.

Several questions still need to be addressed to fully understand the roles of epithelial-derived cytokines in asthma, however. First, what are the immunological triggers that cause the dysregulated activation of airway epithelium and production of epithelium-derived cytokines? One potential break point could be viral infection. The link between viral infection and development and/or exacerbation of asthma is strong in human studies [6]. In an intriguing mouse model mimicking chronic asthma in children, early exposure to respiratory virus induced acute and chronic inflammatory changes mimicking human asthma [19]; airway production of IL-25 is likely involved in this process. Although we do not fully understand how respiratory viral infection in early life affects the functions of airway epithelial cells later in life, these studies provide an excellent starting point for further research into the mechanisms of virus-induced asthma and development of strategies to prevent the inflammatory pathways.

Second, could these epithelial cytokines be effective and safe therapeutic targets for human diseases? The potent abilities of these cytokines to activate and polarize the immune responses to the Th2 pathway suggest that targeting these cytokines may be more efficacious than targeting downstream cytokines, such as IL-5 and IL-13. Recent demonstration of synergistic effects when suboptimal doses of ST2 antibody and CpG-oligodeoxynucleotide (a TLR9 agonist that skews responses toward Th1) were administered in a mouse model of chronic asthma suggests such an approach is promising [83]. The presence of innate immune receptors on the epithelium suggests that targeting these receptors and their ligands has potential both in preventing disease and in ameliorating exacerbations of the established disease. On the other hand, these epithelial cytokines may be critical to maintain immune homeostasis in respiratory mucosa. For example, IL-25 may counterbalance the proinflammatory effects of IL-17 [142]. The epithelium and its cytokines may exist in a delicate balance and caution will need to taken when manipulating these cytokines.

Finally, we need to better understand the immunobiology of IL-25, IL-33, and TSLP and their roles in diseases. While all three cytokines are released by epithelial cells in response to both exogenous and endogenous signals, distinct differences in regulation have been observed. For examples, several triggers are common for all three (e.g. viral infection [109–112]); however, several others uniquely activate release of only one cytokine (e.g. oxidized phospholids and TSLP [98]). Timing and magnitude of release after stimulation also may vary [55]. Accordingly, several key questions need to be addressed in this regard. For instance, in the context of allergic inflammation, what are the relationships among these cytokines? IL-33 and IL-25 are distinguished by their unique activities to activate innate type 2 immune responses. However, as discussed earlier, it is not totally clear to what extent and in which situations IL-25/IL-33 are involved in the generation of Th2-type immune responses. Is IL-25/IL-33 activity more important early in a Th2 response? Is TSLP important later? Further studies are necessary to define the hierarchy and interaction of these cytokines during Th2-type immune responses and inflammation. Questions also remain how the activities of these cytokines, in particular IL-33, are generated. In most cells, IL-33 is

found constitutively in the nucleus as a full-length molecule. As described earlier, IL-33 is considered an "alarmin" that is released by cellular injury or tissue damage. On the other hand, recent studies suggest that IL-33 is released by airway epithelial cells in a non-cytotoxic manner [143, 144]. Thus, it is unclear what are the important physiologic triggers to induce extracellular release of biologically active IL-33 and, if so, what molecular and cellular mechanisms are involved. Finally, what is the fate of these cytokines after they are released into extracellular space? Are soluble receptors involved in regulation of IL-33 similarly to other IL-1-family cytokines? The answers to these questions will be important to fully understand the physiologic and pathologic situations in which these cytokines are engaged. In closing, during the past several years, considerable amounts of information have been generated regarding the roles for IL-25, IL-33 and TSLP in Th2-type immunity. We are now close to understanding the complex mechanisms of chronic Th2-type airway inflammation in asthma and related disorders and to develop novel strategies to treat patients with these diseases.

Acknowledgments

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Highlights

Airway epithelium plays barrier and immune regulatory roles in asthma

Epithelial-derived cytokines, IL-25, IL-33 and TSLP, promote type 2 immune responses

They may create a positive feedback loop promoting airway inflammation and remodeling

Therapy targeting these cytokines may be effective to prevent or attenuate asthma
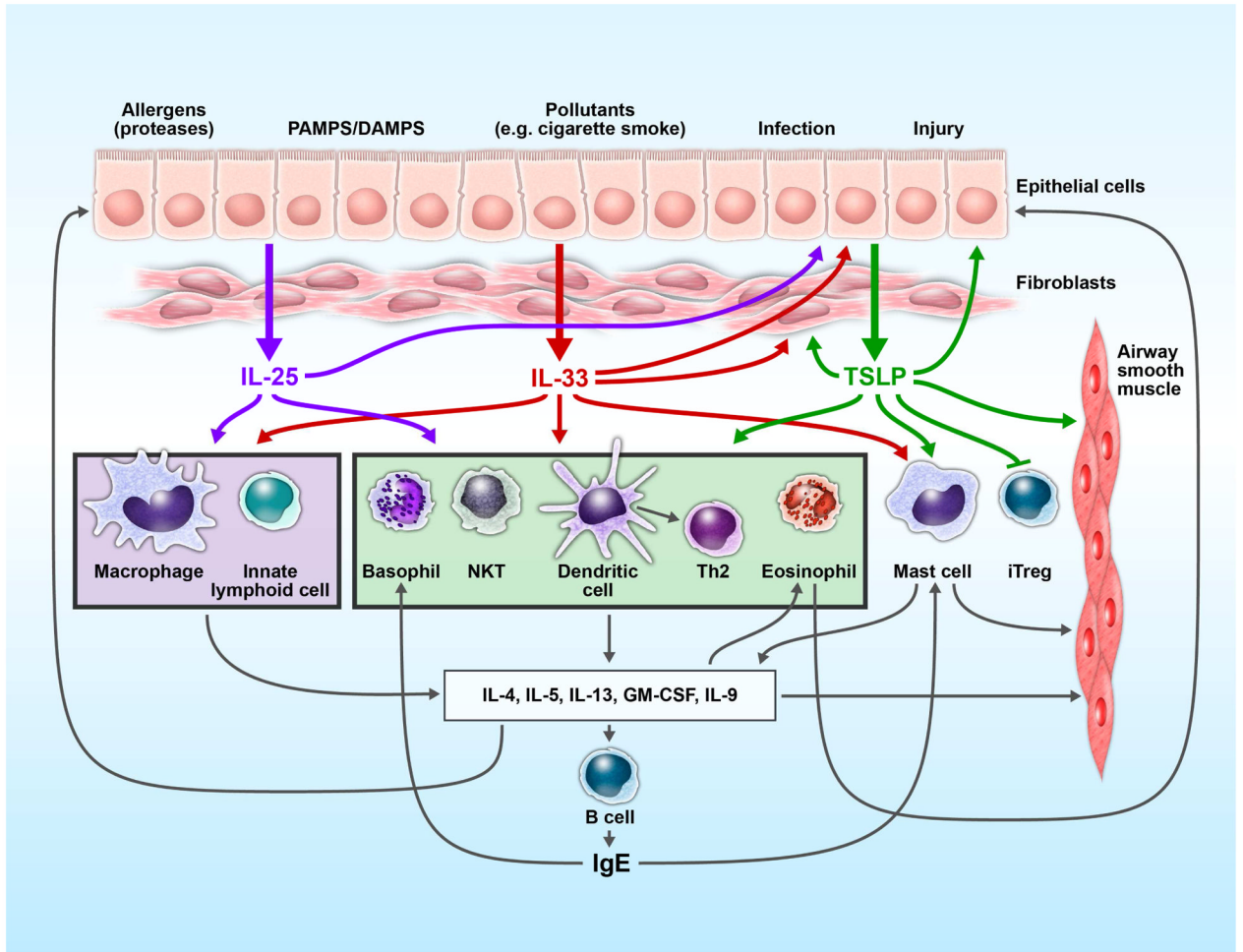
Figure 1.
Interplay between epithelium, immune cells and epithelium-derived cytokines in asthma. Environmental insults (allergens/proteases, microbes, viruses, etc.) stimulate the release of IL-25, IL-33 and TSLP from airway epithelial cells. This triad of cytokines mediates both overlapping and unique effects on immune and structural cells in the airways. They activate DCs, basophils, mast cells, eosinophils, differentiated Th2 cells and NKT cells and drive Th2-type inflammation. Additionally, TSLP induces DC maturation (i.e. upregulation of MHC II and co-stimulatory molecules) capable of polarizing naïve CD4+ cells to the Th2-type. IL-25 and IL-33 induce Th2 cytokine production by innate lymphoid cells and drive macrophages to release IL-13. Th2 cytokines elicit multiple effects on airway tissues, including remodeling, fibrosis and proliferation of smooth muscle cells. Epithelium-derived cytokines, IL-25, IL-33 and TSLP, and the products of Th2-type immune responses provide a positive feedback to airway epithelial cells by enhancing production of mucus and matrix proteins and by stimulating production of cytokines, such as TSLP. Thus, the airway epithelium and its cytokines may play a central role in controlling the immune network within the airway mucosa in asthma.

Table 1

Direct Effects of Epithelium-Derived Cytokines on Immune and Structural Cells

	TSLP	IL-25	IL-33
Immune Cells			
Innate lymphoid cells		induce IL-5, IL-13 [50–52]	induce IL-5, IL-13, GM-CSF [50–52, 55] induce proliferation [51, 55] promote blasting [50]
DC	upregulate CD40, CD80, OX40L [60, 67, 90, 91, 145] drive Th2 polarization [91] drive stronger Th2 polarization when co-primed with antigen [146] induce MDC and TARC [60, 67]	induce IL-5, IL-13 [76]	induce IL-6, TNFα, IL-1β, CCL17 [147, 148] upregulate CD40, CD80, CD86, OX40L, MHC II [147, 148]
Mast cell/mast cell precursors	augment IL-1/ TNFα-induced IL5, IL-6, IL-13, IL-8, GM-CSF, CCL1 [70]		augment SP-induced VEGF [102] activate NF-κB [39] induce IL-5, IL-13, IL-6, IL-8, IL-13, IL-1β, TNFα, MCP-1, eotaxin [47, 149–153] synergistically with ag induce TNFα, IL-6, IL-13, MCP-1, MCP-3, MIP1α [154]enhance survival [151] enhance adhesion [151] cross-activate c-kit receptor [155]
Eosinophil	enhance survival [156] upregulate ICAM-1, CD18 [156] induce IL-6, IL-8, CXCL1, CCL2 [156]	enhance survival [157, 158] induce IL-8, MIP-1β, IL-6, MCP-1 [158] upregulate ICAM-1 [157, 158]	enhance survival [44, 159] induce IL-13, TGFβ, IL-6, IL-8, MCP-1 [44, 45, 99, 103, 160] upregulate ST2, CD11b [99, 159] induce ROS [44] induce degranulation [44] increase adhesion [44, 159]
Basophil	polarize to non-classical subtype [161] upregulate ST2 [161]	upregulate IL17RB post ag challenge [27] induce IL-5, IL-13 [48]	Induce IL-4, IL-5, IL-6, IL-8, IL-9, IL-13 [47, 48, 160, 162–165] release histamine [164] upregulate CD11b, enhance adhesion [165] induce degranulation [165] enhance migration toward eotaxin [165]
Macrophages		induce IL-5, IL-13 [76]	prime naïve to M1 [166] drive M1 to M2 [166] augment LPS-induced IL-6 [139] augment IL-13-mediated killing of *P. muris* [167] enhance IL-13 polarization to M2 [152] upregulate TLR-4, MD2 and augment LPS-induced responses [168]
NK	induce IL-4, IL-13 [169]		induce IFNγ [48, 170]
NKT	induce IL-13 [171]	induce IL-13 [77] with α-galcer, induces IL-4, IL-5, IL-13 [172]	induce IFNγ [170] augment α-galcer -induced IL-4, IL-5, IL-13, TNFα, IFNγ, IL-12 [48] with IL-12 induces IFNγ [48]
naïve CD4+ T	induce proliferation [93] suppress differentiation to iTreg [94]	induce IL-4 [17, 173]	

	TSLP	IL-25	IL-33
Treg	inhibit IL-10 production, suppression [138]		
Th2	induce proliferation [174] induce IL-4 [174] activate Stat5 [175]	induce IL-4, IL-5 [17]	induce IL-5, IL-9, IL-13 [33, 39, 162, 176] chemoattractant [177]
Th9		augment cytokine-mediated IL-9 [78]	
Structural Cells			
Epithelial cells	induce IL-13 [71]	increase gene transcription of eotaxin, RANTES, MUC5ac, TSLP [17, 178]	induce IL-8 [141] increase gene transcription of TSLP, TSLPR [179]
Fibroblast/fibrocytes	produce collagen [106]		induce eotaxin [180]
Airway smooth muscle cells	induce $[Ca^{2+}]_i$ [140] induce eotaxin, IL-8, IL-6 [181]		
Endothelial cells		increase expressed of VEGF and VEGFR [101] increase proliferation [101]	Induce IL-8, IL-6, MCP-1 [141]
Progenitor Cells			
BM Lin−Scal+c-Kit−CD25+			with IL-2 or IL-7, induce IL-5 and IL-13 [56]
Bone marrow progenitors			drive to eosinophils [99]
CD34+ cells	augment IL-33-induced IL-5, IL-13, GM-CSF [107]		induce mast cell maturation [107] induce IL-5, IL-13, GM-CSF [107]