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Sentinels at the Wall: Epithelial-Derived Cytokines Serve as Triggers of Upper Airway Type-2 Inflammation

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Abstract

Recent evidence is demonstrating an expanding role of respiratory epithelial cells in immune surveillance and modulation. Studies are focusing on the earliest events that link epithelial injury to down-stream inflammatory responses. Cytokines produced by and released from respiratory epithelial cells are among these early trigger signals. Epithelial-derived cytokines, namely thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, have come to the forefront of recent investigation. Each of these three cytokines has been implicated in chronic rhinosinusitis (CRS), asthma, and atopy. Here we review studies elucidating the roles of epithelial-derived cytokines in the pathobiology of upper airway disease, with particular emphasis on type-2 inflammatory conditions.

Keywords

type-2 inflammation; mucosal immunity; IL-25; IL-13; CRSwNP

Introduction

The epithelium plays a critical role in the immune system. Different epithelial cell types have specific physical and biochemical functions that help orchestrate innate and adaptive immunological responses. It is well known that ciliated cells, goblet cells, and other epithelial cell types engage the immune system through 'danger signals.' Exogenous danger signals, collectively termed pathogen-associated molecular patterns (PAMPs), stimulate toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors

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to elicit innate immune responses. Likewise, endogenous danger signals called alarmins are released during cell necrosis and apoptosis and can also trigger innate immune defenses.

Recently, research interests in epithelial immunity are honing in on more niche cell types and the specific cytokines they produce. For example, rare cell populations in the gut epithelium (tuft cells) and in the upper airway (solitary chemosensory cells) have been proposed to detect molecules from pathogenic organisms via the canonical taste pathway and release antimicrobial agents to maintain host-pathogen homeostasis.^{1,2} More recent studies investigating gut and respiratory mucosa show that epithelial cells are also capable of secreting specific cytokines that can push inflammation towards a type-2 immune response. In particular, studies implicate a triad of epithelial-derived cytokines, thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33) in driving a type-2 response. Of note, recent attention has also focused on a novel cell type, namely group 2 innate lymphoid cells (ILC2s), which play a crucial role in tipping the scales toward type-2 inflammation downstream of these cytokines.³⁻⁵

In respiratory epithelium, type-2 inflammation is the pathological hallmark of diseases such as chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and allergy. Type-2 inflammation is characterized by ILC2s, T_H2 (CD4+) cells, eosinophils, mast cells, and basophils. Clarifying how epithelial-derived cytokines mediate a type-2 response is key to unlocking a more complete understanding of the pathogenesis of respiratory tract inflammation. Recent studies are now elucidating the earliest stages of epithelial stimulation leading to this mucosal type-2 inflammation. Herein, we will provide a review of a subset of epithelial-derived cytokines and new discoveries to their respective biology with the goal of demonstrating how they may play a role in disease states, especially in the upper airway.

Cellular sources and function of TSLP, IL-25 and IL-33

TSLP, IL-25, and IL-33 are a triad of epithelial-derived cytokines. We will briefly characterize their cellular sources, triggers for release, and downstream function with emphasis on newly discovered mechanisms.

Epithelial-derived TSLP

Thymic stromal lymphopoietin (TSLP), initially identified in 1994 as a cytokine produced by thymic stromal cells, is predominately expressed in sites of barrier function, such as skin, bronchial epithelium, sinonasal mucosa, and intestinal mucosa.⁶ In the upper airway, TSLP is primarily produced by ciliated epithelial cells, mast cells, macrophages, and endothelial cells.⁶ TSLP is an IL-7-like cytokine which binds to a heterodimer receptor, IL-7 receptor α -chain (IL-7R α) and a common γ receptor-like chain (TSLP- γ).⁷ Its expression is triggered by infection of viral, bacterial, and parasitic pathogens.⁸ Inflammatory cytokines (IL-1 β and TNF) as well as T_H2 cytokines (IL-4 and IL-13) induce TSLP in the epithelium via TLRs and cytokine receptor signaling.⁹ In human airway epithelium, TLR3 ligand and infection with rhinovirus were found to be strong stimuli for TSLP expression, via downstream NF- κ B and Interferon Regulator 3 (IRF-3).¹⁰ Mechanical injury and proteases have also been found to induce TSLP release, supporting its function as an alarmin signaling the compromise of epithelial integrity.⁹ In line with the notion that TSLP signals loss of barrier

function, TSLP was shown to be downregulated in cells overexpressing calveolin-1, a factor involved in cell adhesion.¹¹ Hence, TSLP appears to play a role at the initial site of insult exposure to respiratory epithelium. In addition to activating ILC2 cells, it is also well demonstrated that TSLP activates myeloid dendritic cells and increases OX40 ligand receptors on T helper cells which induce maturation of naïve T_H cells toward a T_H2 fate.^{12,13}

Epithelial-derived IL-25

IL-25, the second of the triad, is a member of the IL-17 family. It has been studied for its importance in mucosal site inflammation, particularly for its role in activating ILC2 cells, which serve as a key switch toward the type-2 response and are discussed in further depth below.^{14,15} IL-25 is produced by T_H2 cells, mast cells, eosinophils, and epithelial cells.¹⁶ In epithelial cells, IL-25 is pre-formed and stored in the cytoplasmic compartment.¹⁷ Like TSLP, studies show that IL-25 acts as an alarmin. Epithelial cells release IL-25 in response to stimuli, such as papain, trypsin, and house dust mite antigens, as well as breakdown of epithelial cell-to-cell adhesion.^{17,18} More recently, a specialized group of epithelial cells called solitary chemosensory cells were found to be the major epithelial source of IL-25 in the human upper airway.¹⁹ The receptor for IL-25 is a heterodimer comprised of IL-17RA and IL-17RB. Each component of the receptor is necessary for IL-25 function, as mice that were null for either subunit were not able to mount a type-2 response.²⁰ In addition to eliciting a type-2 response, IL-25 appears to reduce epithelial barrier function and cause tissue remodeling. In an atopic dermatitis model using human skin cells, IL-25 reduced expression of filaggrin, important in skin barrier function, and allowed for increased HSV replication synergistically with IL-4 and IL-13.²¹ In a mouse model, chronic IL-25 exposure contributed to pulmonary fibrosis through IL-13 secreted by ILC2 cells, implicating significant downstream effects on sub-epithelial stromal tissue.²² In humans, high IL-25 was found to be correlated with higher ILC2s.²³ Moreover, IL-13 produced by activated ILC2s has been found to be acting in a feed-forward loop to further propagate IL-25 production.^{19,23}

Epithelial-derived IL-33

First characterized in 2005, IL-33 is the most recently discovered member of the triad of epithelial-derived cytokines.²⁴ IL-33 belongs to the IL-1 family of cytokines, but unlike its family members, IL-33 elicits a type-2 inflammatory response, in a manner more similar to IL-25.²⁴ However, unlike the cytoplasmic storage of IL-25, IL-33 is contained in epithelial and fibroblast nuclei,²⁵ with mast cells and dendritic cells²⁶ serving as minor contributors to IL-33. Studies have suggested the functional role of IL-33 depends on its localization. Nuclear IL-33 exerts transcriptional control through multiple mechanisms, including heterochromatin remodeling and regulation of NF- κ B, influencing IL-6 and IL-8 expression levels.^{27–29} Extracellular IL-33, like its other two compatriots in the triad, also acts as an alarmin. In the setting of epithelial apoptosis or necrosis, nuclear IL-33 is released into the extracellular space where it can initiate its pro-inflammatory effects by signaling through a heterodimer receptor comprised of ST2 and IL-1R accessory protein (IL-1RAP), expressed on T_H2 cells and mast cells.³⁰ Interestingly, it appears that IL-33 function is also controlled in part by a soluble decoy receptor, sST2, found in the serum. In a murine lung injury model,

sST2 overexpression led to decreased airway inflammation through reduction of unbound IL-33.³¹ In humans, GWAS studies revealed that SNPs in the *IL1RL1* locus correlate with sST2 concentration and cardiovascular disease, likely through atherosclerotic inflammatory burden.³² Additionally, caspase-3 and caspase-7 are important for the eventual inactivation of IL-33. While it was initially believed that full-length IL-33 needs to be cleaved by caspase-1 to become biologically active, that concept has since fallen out of favor.³³

Cross-talk within the triad

It is likely that TSLP, IL-25, and IL-33 act partially if not totally in concert as part of the inflammatory milieu. The fact that the cytokines appear to share some of the triggers for release, as discussed above, supports this notion. Yet the exact mechanisms of cross-talk between respective epithelial-derived cytokines are not completely understood. In a murine model of house dust mite airway inflammation, IL-25 appeared to drive IL-33 and TSLP expression.¹⁸ In patients with CRSwNP, expression of all three cytokines were found to be increased in nasal epithelium.³⁴ More recently, Camelo et al. found that the three cytokines acting in concert are required to activate cultured human ILC-2 effector cells and that none of the cytokines alone had an appreciable effect *in vitro*.³⁵ However, further studies are needed to better characterize how each of the cytokines may be interacting with each other and how relative combinations of them might drive specific diseases *in vivo*.

Role of epithelial-derived cytokines in pathogenesis of airway inflammation

Type-2 inflammation is the pathological hallmark of CRSwNP, asthma, and atopy. Studies implicate host and environmental factors leading to dysregulation of epithelial-derived TSLP, IL-25, and IL-33 leading to type-2 inflammation. In this section, we will summarize the research that shows how this triad of cytokines relates to clinical presentation of respiratory disease.

Epithelial-Derived Cytokines and T_H2 Endotype

As the mechanisms behind inflammatory respiratory diseases become clearer, diseases can be classified according to endotypes, which are defined by distinct pathophysiologic mechanisms identified by corresponding biomarkers. This classification scheme has been applied to asthma and, more recently, extended to the upper airway in chronic rhinosinusitis (CRS). CRS is a heterogeneous disease and breaking down this complex disease by endotypes may lead to more targeted therapy.^{36,37} Studies have implicated epithelial-derived cytokines, TSLP, IL-25, and IL-33, in a type-2 predominant eosinophilic endotype in asthma as well as CRS with nasal polyps.³⁸

TSLP in Clinical Respiratory Disease

Considerable evidence demonstrates TSLP involvement in the pathogenesis of inflammatory airway diseases, including CRS,³⁹ allergy,⁴⁰ asthma,⁴¹ and COPD.⁴² In respiratory epithelial cells cultured from asthma patients, TSLP is produced at higher levels compared to those cultured from control patients.⁴³ Two studies have demonstrated that respiratory epithelial cells from asthmatics respond potently to viral double-stranded (ds)RNA by producing higher levels of TSLP compared to epithelial cells from healthy controls.^{44,45} On a genomic

level, certain TSLP polymorphisms are associated with childhood versus adult allergic asthma. In terms of clinical endpoints, there is an inverse correlation between pulmonary function in asthmatics and the expression of TSLP.⁴⁶ Similar findings are emerging in upper airway sinonasal mucosa. For example, TSLP mRNA has been found to be higher in patients with CRSwNP compared to CRS without nasal polyps (CRSsNP).⁴⁷ Moreover, TSLP levels are even higher in CRSwNP in the setting of allergic rhinitis compared to CRSwNP without atopic symptoms.⁴⁰ Additionally, highly eosinophilic and non-eosinophilic CRSwNP seem to have distinct endotypes characterized by differential expression of TSLP and its receptor component IL-7Ra.³⁹

IL-25 in Clinical Respiratory Disease

The role of IL-25 in human airway disease has been demonstrated in a myriad of ways. Among asthmatics, patients with higher IL-25 mRNA levels were also found to be more sensitive to skin allergy testing and exhibited higher eosinophilia, increased IL-13, and greater airway hyper-responsiveness to methacholine challenge, overall supporting a more severe type-2 phenotype.⁴⁸ A similar story is unfolding in the upper airway. Patients with eosinophilic CRSwNP have been observed to express higher IL-25 compared to controls.^{49–51} Ozturan et al examined IL-25 in CRSwNP versus CRSsNP and found no statistically significant difference in IL-25 levels; however, CRSwNP patients were not stratified according to eosinophilia.⁵² More recently Hong et al. stratified CRSwNP patients by IL-25 levels. Patients grouped into the high IL-25 expression cohort had higher CT sinus severity scores, higher nasal endoscopy scores, and higher downstream type-2 cytokine levels.⁵³ In another study, patients with high IL-25 levels were found to have nasal polyps which were more responsive to glucocorticoid therapy,⁵⁴ and this finding was corroborated in an *in vitro* nasal polyp explant model in which steroid exposure reduced IL-25 production.²³

IL-33 in Clinical Respiratory Disease

Lastly, and in the same vein, recent studies have demonstrated the importance of IL-33 in asthma and CRSwNP. Both measured IL-33 levels and select polymorphisms in its receptor gene have been shown to correlate with asthma severity.⁵⁵ In the upper airway, IL-33 expression was higher in epithelial cells obtained from patients with recalcitrant CRSwNP.⁵⁶ In sinonasal epithelial cell cultures derived from patients with persistent nasal polyps, IL-33 was further induced by PAMPs, indicating a potential pathogenic trigger to the aberrant inflammation.⁵⁷ In CRSwNP patients, higher levels of IL-33 also correlated with higher CT sinus severity scores, higher nasal endoscopy scores, and higher downstream T_H2 cytokine levels.⁵³ One group demonstrated that a receptor of IL-33, ST2, is elevated in ethmoid mucosa in CRSwNP patients.⁵⁸ Interestingly, ILC2 cells from diseased mucosa from the same patients with CRSwNP produce more IL-13 in response to stimulation with recombinant IL-2 and IL-33, compared to ILC2s from controls.⁵⁸ Baba et al further demonstrated that ST2-positive eosinophils were increased in the sub-epithelial compartment in CRSwNP patients; however, there was no difference in IL-33 mRNA levels, suggesting receptor sensitivity as a mechanism for eosinophil recruitment.⁵⁹

Novel cell types involved in epithelial-mediated type-2 inflammation

Recently identified cell populations, such as “taster” cells and ILC2 cells, represent niche cell populations that are involved in epithelial-derived cytokine signaling. They have been studied in conjunction with these cytokines.

“Taster” cell populations

Recent studies have shown that rare “taster” cell populations in the epithelium appear to be critical regulators of T_H2 cytokines. In a murine model, “tuft cells” in the intestinal epithelium were found to express signaling components of the canonical taste pathway, including taste-associated G-protein (gustducin) and transient receptor cation channel subfamily M member 5 (TRMP5).^{60,61} Subsequent studies of the murine gut model demonstrated that tuft cells are a source of epithelial IL-25, which promotes a downstream type-2 response via IL-13 and ILC2s in the setting of helminth infection.^{60–62} Interestingly, similar tasting cells called “solitary chemosensory cells” (SCCs) have been described in the sinonasal epithelium.⁶³ SCCs are also rare epithelial cells and like tuft cells express gustducin, TRPM-5, as well as sweet and bitter taste receptors.^{2,64} SCCs are known to play a role in the human innate immune response in the sinuses through stimulation of bitter taste receptors causing release of stored antimicrobial peptides from sinus epithelium.⁶⁵ Recently, Kohanski et al. demonstrated that SCCs are the primary epithelial source of IL-25 in the sinonasal epithelium.¹⁹ Furthermore, similar to murine models, data support that humans have a similar feed-forward loop in which IL-25 from SCCs activate downstream IL-13, that then drives SCC expansion and further enhances IL-25 production²³ (Figure 1).

Group 2 Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) are a type of immune cells of the lymphoid lineage that play an important role in mucosal barrier function. ILCs are grouped according to function, and group 2 innate lymphoid cells (ILC2s) produce significant quantities of T_H2 cytokines: IL-4, IL-5, IL-9, IL-13.^{4,66–68} ILC2s are dependent on GATA-3 transcription factor for proper development and function.⁶⁷ In murine models, ILC2s have been described as a critical switch in mounting type-2 inflammation when respiratory epithelium was challenged with house dust mite, ovalbumin, and glycolipid antigens.^{69,70} In humans, ILC2 cells are stimulated by epithelial-derived cytokines, along with cysteinyl leukotriene, prostaglandin D₂, and TNF family member TL1A.^{71–73} More specifically, a study on ILC2s from human fetal gut found that ILC2s are activated *in vitro* by both IL-25 and IL-33, when co-treated with IL-2.⁷⁴ The same group also demonstrated that TSLP alone can activate ILC2s isolated from human blood through enhanced GATA-3 expression.⁶⁸ However, in a separate study the combination of IL-25, TSLP, and IL-33 are required to activate human ILC2s derived from blood.³⁵ ILC2s have also been implicated in airway inflammation. ILC2s have been found to be enriched in the polyps from CRSwNP patients compared to non-inflamed mucosa from CRSsNP patients and healthy controls.^{23,58,75} However, due to the rarity of resident ILC2s in nasal polyps, isolation of cells has proven challenging and limits experimental study.

Potential targets for intervention

As the molecular and cellular mediators of type-2 inflammation at mucosal sites come to light, we will be better equipped to develop targeted therapies. Here, we briefly discuss novel targets for potential intervention.

Emerging Immunotherapies

Epithelial-derived cytokines are early triggers of the type-2 inflammation underlying asthma and CRSwNP. While monoclonal antibodies have been developed to inhibit downstream targets, namely IgE, IL-5, IL-5Ra, IL-4, IL-13, the upstream targets represent the new frontier. A second advantage of employing biologic therapy against epithelial derived cytokines is the potential to decrease the steroid prescription burden in inflammatory conditions such as asthma and CRS.

In a double-blind, placebo-controlled randomized clinical trial, a monoclonal antibody against TSLP, tezepelumab (AMG157), that is administered subcutaneously decreased allergen-induced bronchoconstriction and reduced eosinophilia in blood and sputum of asthma patients.⁷⁶ In a phase II study, tezepelumab was further found to reduce asthma exacerbation rates and improve FEV1 after 52 weeks of administration to patients with moderate-to-severe asthma.⁷⁷ At the present time, there are no clinical trials targeting epithelial cytokines for the indication of CRSwNP, but focusing on the IL-25 pathway appears to be a promising option. In a murine model, an IL-25 neutralizing antibody decreased nasal polyp burden and reduced polyp mucosa thickness.⁷⁸ In humans, brodalumab, an anti-IL17RA monoclonal antibody has been developed which blocks binding of IL-25 as well as IL17F and IL17A. In a study of 300 patients with moderate to severe asthma, brodalumab did not provide any significant benefit. However, in subgroup analysis, an effect was observed in patients with bronchodilator reversibility, which has warranted further study on this group of patients.⁷⁹

Lastly, in the IL-33 pathway, anti-IL-33 and anti-ST2 monoclonal antibodies reduced eosinophilic airway inflammation and decreased T_H2 cytokines in a murine model.^{80,81} A phase I clinical trial assessing the safety and pharmacokinetics of AMG 282, a monoclonal antibody blocking IL-33 preventing binding to ST2 receptor, has been tested as a potential therapy in atopic asthma and CRSwNP.⁸² These studies represent the beginnings of a new approach to utilizing biologics in early type-2 airway inflammation.

Conclusion

Here we have discussed three important epithelial-derived cytokines, TSLP, IL-25, and IL-33, as summarized in Table 1. Specifically, we reviewed the triad's respective biological function in respiratory mucosa, their role in human airway disease, novel cell types involved in signaling, and potential therapeutic interventions. Further investigation of these epithelial-derived cytokines will afford a more nuanced understanding of type-2 respiratory inflammation. Through this more granular understanding, we may be able to better diagnose and manage CRSwNP, asthma, and allergy.

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Figure 1: Epithelial-derived cytokines IL-33, TSLP, and IL-25 are released in the setting of epithelial injury or pathogenic challenge. These cytokines modulate innate and adaptive immune responses, including activation of ILC2 cells, which are key in eliciting Th2-mediated inflammation.

Table 1:

Summary table of epithelial-derived cytokine pathobiology

	Cellular Source	Receptor	Effector Cells	Clinical Diseases
TSLP	<i>Major:</i> Ciliated respiratory epithelial cells ⁶ <i>Minor:</i> mast cells, neutrophils, macrophages, CD31+ endothelial cells ⁶	TSLPR (heteromer of IL-7R α and TSLP- γ) ⁸³	ILC2 cells, dendritic cells ¹² , Th2 cells ¹³	CRSwNP, asthma, COPD
IL-25	<i>Major:</i> epithelial solitary chemosensory cells ¹⁹ <i>Minor:</i> mast cells, eosinophils, alveolar macrophages, Th2 cells ¹⁶	IL-17Rb ¹⁶	ILC2 cells, anti-gen presenting cells, fibroblasts, eosinophiles, invariant NKT cells ⁸⁴	CRSwNP, asthma, AERD
IL-33	<i>Major:</i> Ciliated respiratory epithelial cells (nuclear) ²⁵ <i>Minor:</i> Fibroblasts ²⁵ , mast cells ²⁶ , dendritic cells ²⁶	IL-33R (heteromer ST2 and IL-1RAP) ³⁰ sST (decoy receptor) ³¹	ILC2, Th2 cells, cells, mast cells, dendritic cells ³⁰	CRSwNP, asthma