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Epithelial Cell Regulation of Allergic Diseases

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Abstract

Allergic diseases, which have escalated in prevalence in recent years, arise as a result of maladaptive immune responses to ubiquitous environmental stimuli. Why only certain individuals mount inappropriate type 2 immune responses to these otherwise harmless allergens has remained an unanswered question. Mounting evidence suggests that the epithelium, by sensing its environment, is the central regulator of allergic diseases. Once considered to be a passive barrier to allergens, epithelial cells at mucosal surfaces are now considered to be the cornerstone of the allergic diathesis. Beyond their function as maintaining barrier at mucosal surfaces, mucosal epithelial cells through the secretion of mediators like IL-25, IL-33, and TSLP control the fate of downstream allergic immune responses. In this review, we will discuss the advances in recent years regarding the process of allergen recognition and secretion of soluble mediators by epithelial cells that shape the development of the allergic response.

Keywords

Pattern-recognition receptor (PRR); Toll-like receptors (TLRs); House dust mite (HDM); Chitin; IL-33; IL-25; TSLP

Introduction

Recent discoveries have highlighted the key role of the epithelium in sensing several components within allergenic sources and regulating the outcome of the allergic response [1]. While allergens are innocuous to most non-allergics, in susceptible individuals, allergenicity may arise from a mistaken identity wherein the host responds to certain components of allergenic sources as potential threats. These moieties are known as pathogen-associated molecular patterns (PAMPs) and are sensed by host pattern-recognition receptors (PRRs). Thus, while a healthy mucosal barrier can maintain relative immune quiescence to daily contact with multiple sources of allergens, dysregulated mucosal sensing of these environmental stimuli in susceptible individuals can trigger aberrant type 2 responses.

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Drs. Gour and Lajoie declare no conflicts of interest relevant to this manuscript.

Environmental Triggers

Despite the unique properties of protein allergens, it is now clear that allergic inflammation is not limited to the biological actions of allergens themselves but is strongly influenced by epithelial sensing of abundant non-protein components in allergenic sources like chitin, lipids, and endotoxin. Dysregulated sensing of chitin, lipids, and endotoxins is likely a major determinant in the development of allergic responses.

Chitin

Chitin, a polymer of β1-4 linked *N*-acetylglucosamine, is the major constituent of the exoskeleton of crustaceans, helminthes, fungi, and insects, making it one of the most abundant biopolymers. Its presence in most sources of allergens is thought to be a driver of aberrant Th2 responses. Barrier epithelial cells can directly respond to chitin particles to produce cytokines [2•]. While there has been considerable research regarding the role of chitin on the allergic response, the mechanisms by which chitin is sensed remains unclear. While there is no recognized chitin receptor, several PRRs have been shown to bind chitin or be necessary for its biological action on mammalian cells. Recent studies have indicated that recognition of fungal (*Candida albicans*) chitin required NOD-2, TLR9, and the mannose receptor in order to drive IL-10 from peripheral blood mononuclear cells (PBMCs) [3]. FIBCD1, a transmembrane protein found on the gut epithelium can bind chitin [4], similarly to the secreted gut epithelium-associated C-type lectin RegIIIg [5].

Although mammals cannot synthesize chitin, the epithelium as well as macrophages expresses chitin-cleaving enzymes (chitinases), such as acidic mammalian chitinase (AMCase) and chitotriosidase (*CHIT1*) [6–8].

It is thought that chitin particles are broken down by chitinases to form smaller sized, mostly innocuous, fragments. In fact, chitin size appears to be central to the elicitation of immune responses in the lungs, where large fragments (>70 μm) are generally considered to be biologically inert, the midsize (40–70 μm) are proinflammatory, and small-sized chitin can induce anti-inflammatory responses characterized by IL-10 production [9]. In mice, exposure to medium-sized chitin particles induces epithelial-associated type 2 cytokines TSLP, IL-25, and IL-33, and the subsequent accumulation of IL-13-producing type 2 innate lymphoid cells (ILC2), eosinophils, and alternatively activated macrophages (AAM) [10].

Consistent with the concept that chitin must be enzymatically broken down to avoid aberrant type 2 responses, mice deficient in the enzymatically active AMCase (AMCase-ED) have an exacerbated allergic airway inflammation in response to house dust mite (HDM) extract [11•]. Bone-marrow chimera studies showed that AMCase in structural cells, more so than hematopoeitically expressed (macrophage) AMCase, is central in mediating enhanced IL-33 and eosionophilia following allergen exposure [11•]. Specifically, administration of chitin in the airways of mice leads to eosinophilia and mucus production. However, these effects were significantly more severe in AMCase-ED mice suggesting that uncleaved chitin leads to heightened pathophysiology. Surprisingly, only large-sized chitin could induce IL-33 in the BAL, which was more pronounced in AMCase-ED mice but small size could not. The authors claimed that chitin or chitin-containing dust mite extracts activates caspase-1 which

in turn activates caspase-7 which then cleaves and inactivates IL-33 thus leading to resolution of type 2 inflammation [11•]. These findings are in contrast to another report demonstrating a lack of effect in AMCase KO mice in the allergic phenotype in either acute or chronic model of dust mite exposure [12]. The mechanism behind these differences are unclear but may involve the fact that one study used an intact but enzymatically inactive AMCase that can still bind chitin [8], versus one in which AMCase protein expression was abolished [12], thus suggesting that while AMCase's best-known function is to cleave chitin, it may play other roles in chitin biology. Moreover, it is possible that the other active chitinase, chitotriosidase (*CHIT1*), has a redundant role in the absence of AMCase; its expression was reportedly detected in the lungs of AMCase KO mice [12] but not in AMCase-ED mice [11•]. However, the role of chitotriosidase CHIT1 is yet to be explored in the context of allergic diseases.

Endotoxin

Microbial (gram-negative bacteria)-derived endotoxins or lipopolysaccharide (LPS) are potent modulators of the allergic immune response. At mucosal surfaces, LPS complexes with CD14/MD-2 triggering Toll-like receptor-4 (TLR4)-mediated downstream signaling involving Myd88 dependent or independent NF-kB activation. TLR4 is strongly expressed by antigen-presenting cells (APCs) like dendritic cells (DCs) and macrophages, but it is also found in many nonhematopoietic cells like the epithelium. Epithelial TLR4 is generally found at low levels and often intracellularly within endosomal compartments but can readily reach the cell surface upon sensing of microbes [13]. However, airway epithelial cells are generally thought to be hyporesponsive to endotoxins due to low or absent MD-2 [14]. Because endotoxins are highly prevalent in most environments and naturally found in the oral and nasal cavities of humans [15], this is thought to prevent aberrant mucosal inflammation from exposures to this ubiquitous environmental component.

While the role of endotoxin exposure on allergic diseases appears complex, several human studies have found that increased microbial exposure associated with farm living was protective against the development of allergic diseases like hay fever or asthma. These findings form the basis of the hygiene hypothesis, where lack of early childhood exposure to microbial cues increases one's predisposition to develop allergic diseases later in life [16]. Nevertheless, human and mouse studies have been conflicting as to the role of endotoxin sensing in allergic inflammation. Epidemiological findings show that household LPS levels are inversely correlated with allergies in cities [17, 18], yet others find a positive association between LPS and wheezing in children [19]. Occupational exposure to higher endotoxin levels is associated with nonallergic asthma in animal farmers [20, 21]; however, prevalence of allergic (atopic) asthma was decreased with endotoxin exposure [18, 22, 23].

The mechanisms by which endotoxin protects against allergic diseases remain unclear. Still, studies provide evidence that environmental microbial exposure may favor a Th1 over a Th2 immune response. In farm-raised children, PBMCs produce higher levels of the Th1 cytokines (IL-12, IFNg), as well as the immunosuppressive cytokine IL-10 compared to nonfarm children [24]. However, recent studies demonstrate the central role of the epithelium in mediating the protective effects of endotoxins on allergic inflammation.

Exposure to a low dose (100 ng/ml, every other day for 2 weeks) or a single high dose (1 μg) of endotoxin before sensitization to HDM was shown to protect against experimental allergic airway inflammation [25•]. Specifically, endotoxin/farm dust exposure activates the ubiquitin-modifying A20 enzyme (*Tnfaip3*) in lung epithelial cells. A20 is an essential negative regulator of NF-kB signaling downstream of TLR stimulation as *Tnfaip3*-deficient mice die of spontaneous inflammation, but can be rescued if made deficient in the TLR signaling molecule MyD88 ($Tnfaip3^{-/-}Myd88^{-/-}$ double KO) [26]. Epithelial activation of A20 is necessary for the protective effects of LPS on allergen-induced lung inflammation and is abrogated in mice in which *Tnfaip3* has been specifically deleted in the lung epithelium. A20 protects against aberrant Th2 inflammation by suppressing HDM-induced epithelial release of mediators like GM-SCF and CCL20 and subsequent decrease in the recruitment of DCs to the lungs and draining lymph nodes. Moreover, authors reported an association of a single nucleotide polymorphism (SNP) in *TNFAIP3*, which has been linked to various autoimmune disorders, to increased risk for asthma and eczema. This suggests that the beneficial effect of microbial exposure depends on the host genetics; while some A20 SNPs in regulatory regions are associated with decreased expression, others are in its coding region and approximately 5 % of individuals have a faulty A20.

Intriguingly, chimeric mice studies by the same group had previously reported that TLR4 activation of airway structural cells was absolutely required for induction of allergic asthma in mouse models utilizing LPS and dust mite extract [27]. Lack of *Tlr4* on airway structural cells was sufficient to nearly abrogate HDM-driven eosinophilia and Th2 cytokine production (IL-5 and IL-13) as well as the production of IL-25 and IL-33 in the BAL [27]. In addition, in a model where *Tlr4* was deleted specifically in the airway epithelium, mice showed a partial attenuation of HDM-mediated eosinophilic inflammation and IL-33 production [28]. However, the effect of epithelial *Tlr4* deletion on mucus production and airway hyperresponsiveness was not determined [28]. Sensing of endotoxins by the epithelium is generally considering low because epithelial cells poorly express key TLR4 signaling components like MD-2. However, the *Der p 2* allergen within HDM, a structural homologue of MD-2, can mimic its function and induce TLR4 signaling in epithelial cells in the absence of MD-2 [29]. In support of these data, as NF-kB is central to endotoxin signaling, mice challenged with HDM in which NF-kB activation was abrogated in the lung epithelium showed partially decreased pulmonary eosinophils and IL-13 but displayed no improvement in mucus metaplasia or airway resistance [30]. While some reports find a pro-allergic role for endotoxins, they nevertheless demonstrate that in mice, triggering of TLR4 or downstream NF-kB, upon exposure to complex allergens, may not be sufficient to cause all the cardinal manifestations of asthma. This may explain why most individuals do not become allergic or asthmatic after allergen exposure.

Taken together, these studies demonstrate that mucosal epithelial cells will generate a protective or, at most, a restrained inflammatory response to endotoxins in sources of allergens. This supports the concept that healthy epithelial cells remain hyporesponsive to constant contact with common aeroaller gens. Furthermore, it can be speculated that components other than endotoxins, like plant-derived arabinogalactans [31••] in farm dust extracts, confer protection against allergic asthma. This, in conjunction with other moieties

in allergen extracts, may alter the balance of signals received by mucosal epithelial cells and lead to different immunological outcomes.

Lipids

While several potent allergens are characterized as lipid-binding proteins such as *Der p 2* from HDM and *Bet v 1* from birch pollen [32], sources of allergens themselves contain a variety of lipids that can have both immunomodulatory and immunostimulatory functions. Lipid processing and presentation is typically associated with the non-classical MHCI-like CD1 molecules expressed by DCs and presented to invariant natural killer T (iNKT) cells, via CD1d and to mucosal-associated MR1-restricted invariant T cells via CD1a, CD1b, and CD1c [33]. New findings have shown that intestinal and bronchial epithelial cells express CD1 proteins and are able to present lipid antigens to lymphocytes [34, 35], suggesting the possibility that the epithelium can directly activate lymphoid cells, bypassing the need for DCs. In a model of colitis, dendritic cell CD1d-driven signals drive NKT-mediated intestinal inflammation [36••]. However, engagement of CD1d on intestinal epithelial cells lead to secretion of the antiinflammatory cytokine IL-10 and the dampening of intestinal inflammation [36••]. These findings raise the interesting possibility that epithelial CD1 may also engage lipids within allergenic extracts and control aberrant inflammation at mucosal surfaces.

Tasting the Allergen

The discovery of functional extraorally expressed taste receptors has generated significant excitement because of their novel role as regulators of innate immunity. Both sweet and bitter taste receptors are expressed by gut and lung epithelial cells [37–40], where they are thought to form a novel pathogen detection pathway. Sweet taste receptors (TIR) can respond to sugars like glucose and sucrose and will detect varying glucose concentration in the respiratory mucosa. While there is not any endogenous ligand(s) recognized for bitter taste receptors (TAS2Rs), they can detect inhalant chemicals, toxins (sodium thiocynate, acetylthiourea etc.), and bacterial products (lactones). Bitter taste receptors are G-protein-coupled receptors and have been identified on several structural cells of the airways like smooth muscle cells and bronchial and sinonasal epithelial cells and on the cilia itself where their activation was shown to enhance ciliary beat frequency and nitric oxide production, facilitating clearance of toxins [41]. Activation of TAS2Rs was reported to relax smooth muscle contraction [42••], and application of various bitter compounds (choloroquine, denatonium, dextromethorphan) was shown to inhibit IgE dependent production of histamine and prostaglandins from cord-blood mast cells [43].

Expression of several TAS2Rs is upregulated in allergic nasal epithelial cells compared to controls, and while they are constitutively expressed by the respiratory epithelium, they are upregulated by exposure to Th2 cytokines (IL-4, IL-5, and IL-13) [44]. However, signaling via bitter taste receptors may be protective. In mice, bitter tastants were shown to relax bronchial smooth muscle and decrease allergen-induced airway resistance [42••]; also, application of various bitter compounds to patients lead to a decrease in visual analog scores (VAS) for rhinorrhea, nasal obstruction, and sneezing [44]. A recent study also reported an association between SNPs in *TAS2R14*, increased bronchodilator response, and lower

asthma control test (ACT) scores in a Korean asthma cohort [45]. Nevertheless, it remains to be determined whether differences in expression or function of taste receptors play a key role in the manifestations of allergic diseases, and if signaling via TIRs or TAS2Rs can be used as a therapeutic approach. Furthermore, because microbes can secrete compounds sensed by mammalian taste receptors, it is conceivable that allergen extracts contain ligands that are able to activate these receptors and regulate the allergic response.

Epithelial Mediators

In susceptible individuals, exposure to environmentally common sources of allergens can lead to the aberrant production of IL-33, IL-25, and TSLP. The last decade of research has lead to an explosion of research on the role of these epithelial-derived innate cytokines in driving the allergic response. However, the relative importance of each of these mediators appears to differ in different models of Th2 inflammation.

IL-33

Discovered about a decade ago, IL-33 has been shown to have profound effects in driving aberrant Th2 responses. Once released, IL-33 binds to its receptor (IL-33R), which is comprised of ST2 (also known as IL1-RL1 or IL-1R4) and the IL-1 receptor accessory protein (IL-1RAcP/IL-1R3). Several polymorphisms in the *IL33* and *IL1RL1* loci have been reproducibly associated with allergic airway diseases [46, 47]. Moreover, levels of IL-33 are especially elevated in asthmatics and patients with chronic rhinosinusitis or allergic rhinitis [48–51]. IL-33 mediates its Th2-promoting effect via signaling to various immune cells, like T cells, mast cells, DCs, and ILC2. IL-33 is known to be a potent driver of IL-5 and IL-13 in mast cells and ILC2, and for this reason, it is thought to be central in initiating and amplifying aberrant type 2 innate responses. Consistent with the importance of IL-33 as a major driver of Th2 responses, administration of IL-33 is sufficient to cause AHR, whereas blockade of IL-33 signaling significantly decreases AHR in influenza- and HDM-exposed mice [52, 53]. Moreover, IL-33 is critical for the development of OVA and peanut-mediated anaphylaxis in mice. While IL-33 is necessary for body temperature drop during systemic anaphylaxis, it remains unclear whether this is due to the effect of IL-33 on IgE production, as *Il33* KO mice show no defect in IgE [54], whereas *Il1rl1* KO mice have decreased IgE [52].

Although IL-33 can be secreted by macrophages, the epithelium is the primary source of IL-33 in humans and in mouse models of allergic inflammation [48, 55–57]. Initially thought to be only released from dying cells, IL-33 has been shown to also be secreted without affecting cell viability in response to various stimuli like dust mite, fungal extract, and biomechanical stress [58]. IL-33 is uniquely expressed and regulated, and it is located in the nucleus bound to chromatin where it is thought to act as a transcriptional regulator as indicated by its association with histone methyltransferases [59] and histone deacetylase 3 (HDAC3) [60]. While nuclear IL-33 is regulatory by nature, the secreted form is a potent driver of type 2 responses [61]. Interestingly, upon contact with allergens (HDM and *Alternaria alternata* extracts), IL-33 is rapidly secreted (within minutes) *in vivo* and *in vitro* from pre-formed stores from primary bronchial human epithelial cells with no change in transcript levels [62•, 63••].

While little remains known about the cellular pathways that control IL-33 production and its rapid release by the epithelium, recent findings have shed some molecular insight. ATP production, following allergen exposure, signals through the purinergic receptor P2Y2 to activate DUOX1 (a NADPH oxidase) [62•], followed by activation of Src/EGFR, leading to release of IL-33 from epithelial cells. Moreover, IL-33 secretion was blocked by inhibiting nuclear export (leptomycin B), indicating that nuclear IL-33 may be rapidly processed for export, and secretion upon sensing of allergen [62•]. Moreover, as DUOX1 is aberrantly expressed by airway epithelial cells from asthmatics [62•], this may explain elevated IL-33 in asthma. In contrast, in response to house dust mite, the Rac-1 GTPase inhibits IL-33 production, and mice lacking *Rac1* in airway epithelial cells have exacerbated dust mitedriven allergic airway inflammation [57]. In addition to being a central source of IL-33, the bronchial epithelium, especially basal epithelial cells in mice and men, strongly express ST2 [64•] and respond to IL-33 by producing IL-6, IL-8, and MCP-1 which can further promote allergic inflammation [65].

IL-33 Deactivation—Multiple findings suggest that the IL-33-IL-33R axis can be inactivated in a variety of ways, and it is interesting to speculate whether pathways of IL-33 deactivation may also be compromised in allergic individuals in parallel to enhanced production of IL-33. In addition to the transmembrane ST2, soluble ST2 (sST2) is produced by the epithelium and functions as a decoy receptor, neutralizing the effects of IL-33 [66]. Consistent with the proposed protective effects of sST2, vitamin D is a potent inducer of sST2 production in bronchial epithelial cells [67], and vitamin D insufficiency is associated with several allergic diseases [68]. Surprisingly, sST2 is elevated in several diseases like asthma and ulcerative colitis and may suggest an attempt to control aberrant IL-33.

IL-33 signaling can also be controlled via downregulation of its cognate receptor ST2 (IL-1RL1), unlike its signaling partner, IL-1RAcP, that appears to be expressed at basal levels in various cells. Recent studies reported that ST2 can be downregulated after IL-33 stimulation. Specifically, IL-33 stimulation causes GSK3b-dependent phosphorylation of ST2 that promotes its association with FBXL19 (an E3 polyubiquitin ligase) facilitating its ubiquitination-dependent proteosomal degradation [69]. On the other hand, the GOLgi Dynamics (GOLD)-domain-containing protein TMED1, which is involved in vesicular trafficking of proteins, physically associates with ST2 facilitating IL-33 responses [70]. Additionally, IL-33 itself can be deactivated via multiple mechanisms. IL-33 released from dying cells can be deactivated by apoptotic caspase-3 and caspase-7 and not inflammatory-associated caspases (casp1, casp4, and casp5) [71]. However, active caspase-3 can be actively released from healthy cells after LPS stimulation [72] and suggests the possibility that IL-33 released via non-cell death pathways can also be cleaved and deactivated. In addition, IL-33 can be rapidly oxidated by the extracellular environment (within 1–4 h) resulting in suppression of its biological activity. The oxidative process drives the formation of two disulfide bridges resulting in a conformational change that prevents its binding to ST2 [63••]. These data highlight a novel level of cytokine regulation, and the newfound importance to measure both active and inactive (disulfide bridge bonded) forms of IL-33.

IL-25

Discovered as the fifth member of the IL-17 cytokine family, IL-17E or IL-25 is a potent driver of Th2 responses at multiple mucosal surfaces. IL-25 has important roles in mediating type 2 responses in the skin, gut, and lungs. Barrier epithelial cells secrete IL-25 in response to multiple allergens [73], IL-25 is necessary for both allergen-induced airway inflammation and hyperresponsiveness [74, 75] and is sufficient to drive aberrant Th2 inflammation in the lungs. However, these effects are largely dependent on the ability of IL-25 to induce IL-13. Consistent with this, allergen exposure has been shown to upregulate IL-25R (IL-17RB) on dendritic cells in asthmatics [76]. IL-25 has been show to activate DCs by upregulation of co-stimulatory molecule expression (CD80, CD86) [77] and Jagged-1 [78], which promotes the differentiation of naïve T cells into Th2 lineage. Moreover, airway epithelial cells can respond to IL-25, and through an autocrine-paracrine mechanism, become activated to secrete the leukocyte chemoattractants CCL5 (RANTES) and CXCL1 (GROa) [73]. In a subset of Th2-high asthma patients, epithelial IL-25, and not IL-33 or TSLP, is particularly elevated and predicts responsiveness to corticosteroids [79]. IL-25-high, as opposed to IL-25-low asthmatics have greater eosinophilia and elevated markers associated with airway remodeling like basement membrane thickness and mucin gene expression (*MUC5AC*) [79]. This is consistent with several findings using primary human airways cells and in mice that IL-25 is a potent driver of extracellular matrix deposition [74]. Elevated IL-25 further enhances collagen deposition in the lungs by promoting IL-13 from ILC2 [80].

In addition to its role in allergen-induced models, IL-25 plays a role in viral-exacerbations of asthma as asthmatic bronchial epithelial cells secrete increased levels of IL-25 post-rhinovirus infection as compared to non-asthmatic controls [81]. Moreover, atopic asthmatics secreted higher levels of IL-25 in nasal mucosal fluid post RV-16 infection, compared to non-asthmatics [81]. Further, in a mouse model of rhinovirus-induced asthma exacerbation, blockade of the IL-25 receptor, IL-17RB, attenuates allergic pulmonary inflammation and viral load [81].

IL-25-Producing Tuft Cells—For more than 50 years, the presence of brush cells, now known as tuft cells was reported in the lungs [82] and gut [83]. Several simultaneous reports have linked the importance of these taste-chemosensory epithelial cells in promoting type 2 immune responses. Lamina propria tuft cells constitutively express IL-25 (and not IL-33 and TSLP); however, they readily expand following helminth infection [84]. Tuft cell-derived IL-25 is crucial for the optimal recruitment of IL-13-producing ILCs, necessary for worm clearance [84, 85]. Interestingly, IL-25 producing tuft cells as well as IL-33-producing basal cells and are known to have stem-cell like properties indicating that these cells/cytokines may have regenerative functions, in addition to promoting allergic inflammation [86•].

TSLP

Epithelial cells of the human airways, gut and skin are a central source of TSLP. Its expression is induced by multiple environmental stimuli, like allergens, respiratory viruses, diesel exhaust, microbes, and helminth [87]. Moreover, specific engagement of innate sensors like TLR3, TLR5, and TLR2-TLR6 drives TLSP secretion [88]. Its aberrant expression at multiple barrier sites is thought to be a unifying factor in the development of

multiple allergic disorders. Elevated TSLP production is observed in multiple allergic diseases like atopic dermatitis, asthma, and food allergies. In addition to its dysregulated expression in allergy, several *TSLP* SNPs have been associated with allergic asthma, atopic dermatitis, and eosinophilic eosophagitis [89]. In fact, recent studies highlighted an important role for TSLP in the atopic march, a phenomenon where already allergic individuals in early life will be predisposed to develop another allergic disorder. Atopic dermatitis (AD), whose onset is within first 6 months of birth in 45 % of the cases, is thought to predate the development of subsequent allergic diseases (allergic rhinitis, asthma) in atopic individuals [90]. While the molecular mechanisms behind the atopic march phenomenon have remained elusive, recent studies have reported that mice sensitized with ovalbumin in addition to intradermal TSLP, and not IL-25 injections, developed heightened type 2 responses in the lungs following intranasal challenges with OVA, and this effect seemed dependent on CD4+ T cells [90]. While T cells can directly respond to TSLP [91], it is thought that its Th2-promoting effect is mostly driven as a result of its ability to prime DCs to drive Th2 differentiation [92]. Moreover, recently, TSLP has been shown to expand a population of spleen progenitor-like cells resembling granulocyte-monocyte precursors (GMP) and can drive their differentiation into various cells of the myeloid lineage that serve as APCs [93].

While the precise mechanisms by which TSLP can drive allergic airway disease are unclear, it is possible that excess production of TSLP via skin exposure may facilitate allergic manifestations in the lungs. Interestingly, intradermal exposure to TSLP is sufficient to break tolerance to oral ovalbumin and can lead to the development of allergic airway disease when mice are challenged intranasally to OVA [90]. Consistent with these experimental observations, antibody-mediated blockade of TSLP resulted in improvement of lung function and allergic inflammation in primates [94] and humans [95•]. These data may suggest that sensitization to innocuous allergens in the presence of elevated TSLP levels in atopic individuals leads to the atopic march. Moreover, TSLP can drive aberrant type 2 responses and AD-like disease independent of Th2 cells, through TSLP-dependent recruitment of ILC2. ILC2 are enriched in skin lesions from patients with atopic dermatitis. Consistent with the central role of TSLP in the allergic skin, in a mouse model of AD, *Il33*$^{-/-}$, *Il25r*$^{-/-}$, or *Rag*$^{-/-}$ (which are devoid of T or B cells), mice did not display a decrease in skin-ILC2s; however, loss of TSLP signaling protected against skin pathology [96]. In addition to directly modulating IL-13-producing cells (Th2/ILC2), TSLP can promote Th9 cells, which also have key roles in promoting allergic responses. In mice, TSLP can directly drive IL-9 production from Th9 cells to further drive allergic airway inflammation [97], and there is a positive correlation between IL-9 and TSLP concentration in the serum of infants with AD [97].

Intriguingly, TSLP has roles beyond just an effector cytokine targeting immune cells. TSLP released from keratinocytes can drive severe scratching behavior in mice lacking T and B cells via direct activation of a subset of TSLP receptor-expressing neurons in the dorsal root ganglion [98]. Suggesting that some allergic disease manifestations, like AD-induced itch, may be elicited by a direct epithelial-peripheral nervous system crosstalk.

Taken together, IL-33, IL-25, and TSLP have a central role in driving both aberrant innate type 2 responses though their actions on mast cells and ILC2, and in the initiation of Th2 cells by priming DCs. However, recent research suggests that they may have a limited function in maintaining allergic inflammation in mice. As expected, the concomitant absence of IL-33, IL-25, and TSLP signaling significantly impairs the initiation of type 2 inflammation; however, these combined blockade of these cytokines have minimal impact in reducing markers of already established HDM-driven allergic inflammation [99•]. This may suggest that established allergic diseases driven by memory Th2 cells might be regulated via distinct pathways.

Conclusions

It is now clear that epithelial cells at mucosal surfaces play a dominant role in allergic diseases. The healthy epithelium is key to maintaining mucosal homeostasis and may potentiate immune tolerance to often-encountered allergens. There is now mounting evidence that in allergic individuals, susceptibility to develop aberrant type 2 inflammation to innocuous environmental allergens may not only be due to upregulated pro-allergic mechanisms but also because of repressed or faulty protective pathways.

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