Epithelial cell–derived cytokines: more than just signaling the alarm

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The epithelial cell–derived cytokines thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 are central regulators of type 2 immunity, which drives a broad array of allergic responses. Often characterized as "alarmins" that are released by the barrier epithelium in response to external insults, these epithelial cell–derived cytokines were initially thought to act only early in allergic inflammation. Indeed, TSLP can condition dendritic cells to initiate type 2 responses, and IL-33 may influence susceptibility to asthma through its role in establishing the immune environment in the perinatal lungs. However, TSLP, IL-33, and IL-25 all regulate a broad spectrum of innate immune cell populations and are particularly potent in eliciting and activating type 2 innate lymphoid cells (ILC2s) that may act throughout allergic inflammation. Recent data suggest that a TSLP/ILC axis may mediate steroid resistance in asthma. Recent identification of memory Th2 cell subsets that are characterized by high receptor expression for TSLP, IL-33, and IL-25 further supports a role for these cytokines in allergic exacerbations. There is therefore growing interest in developing biologics that target TSLP, IL-33, and IL-25. This Review provides an overview of TSLP, IL-33, and IL-25 and the development of blocking antibodies that target these epithelial cell–derived cytokines.

The epithelial lining of the skin, gut, and lungs has long been known as a protective barrier against infection and physical or chemical injury. As the primary organ that senses the external environment, it is now clear that the barrier epithelium also functions as a key sensor and integrator of environmental cues. Allergic diseases encompass a wide breadth of pathological immune responses to otherwise innocuous antigens that are encountered at barrier sites of the body. These responses, called type 2 immune responses, also provide protection against helminth infections. In allergic diseases, type 2 inflammation can drive atopic dermatitis (AD) in the skin; food allergies and eosinophilic esophagitis (EoE) in the gastrointestinal tract; or asthma, allergic rhinitis, and chronic rhinosinusitis within the respiratory system. The prototypical type 2 response is characterized by induction of Th2 cells; B cell production of IgE; activation of specific innate cell populations such as type 2 innate lymphoid cells (ILC2s), eosinophils, mast cells, and basophils; and production of type 2 cytokines such as IL-4, IL-5, IL-9, and IL-13 by innate and adaptive immune cells. The itch response, mucus production, and bronchoconstriction may also be components of the type 2 allergic response.

Regulatory T cells (Tregs), which are important in maintaining immune homeostasis, also regulate type 2 immunity at barrier surfaces. Mice that lacked the CNS1 gene regulatory region at the *FOXP3* locus, which is required for peripheral induction of Tregs, spontaneously developed type 2 inflammation within the gastrointestinal tract and lungs (1). Mice whose Tregs lacked expression of the transcription factor RORα exhibited exaggerated type 2 skin inflammation in models of AD (2). This exaggerated inflammation in RORα-deficient Tregs may have been in part due to decreased expression of death receptor 3 (DR3; also known as TNF receptor superfamily member 25, or TNFRSF25) on Tregs. DR3 on Tregs can bind the ligand TL1A (also known as TNF superfamily member 15, or TNFSF15) and may sequester TL1A to restrain TL1A-driven inflammation by Th2 cells and ILC2s. Additional data also suggest that Tregs can regulate ILC2 function through ICOS-ICOSL interactions and production of IL-10 and TGF-β (3).

In epithelial regulation of allergic type 2 responses, three cytokines — thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 — have emerged as critical mediators of type 2 inflammation. These cytokines alert the immune system to external insults and regulate tissue restoration and repair after injury. While our understanding of how these cytokines function initially focused on their roles early in type 2 responses, emerging data suggest that these three cytokines provide important tissue-specific signals to both innate and adaptive cell populations throughout type 2 inflammation. TSLP, IL-33, and IL-25 may therefore be important mediators of inflammation during allergic disease exacerbations and may prove to be key targets for therapeutic intervention even after disease is well established. This Review provides an overview of the regulation and function of TSLP, IL-33, and IL-25. We also discuss the current status of the development of treatments that target TSLP, IL-33, or IL-25.

TSLP

TSLP is a member of the IL-2 family of cytokines that was initially identified as a pre–B cell growth factor (4). Epithelial cells in the lungs, skin, and gastrointestinal tract are thought to be the primary source of TSLP during both homeostatic and inflammatory condi-

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tions, although dendritic cells (DCs), basophils, and mast cells can also express TSLP (5–9). TSLP expression and release from epithelial cells is increased in response to a broad array of stimuli, including mechanical injury, infection, inflammatory cytokines, and proteases such as trypsin and papain (6, 10, 11). Two main isoforms of TSLP have been described in mice, but the functional consequence of these variants is unknown. In humans, a short isoform appears to be expressed in basal conditions, whereas a longer isoform is induced by inflammatory stimuli (12). Cleavage of human TSLP by serine proteases may also regulate TSLP protein levels or function, although it is unclear whether a similar regulatory mechanism exists in mice (13, 14). TSLP genetic variants and high levels of TSLP expression have been linked to atopic diseases such as AD, asthma, allergic rhinoconjunctivitis, and EoE (15). TSLP overexpression has also been reported in Netherton syndrome, a genetic disease caused by mutations in SPINK5 that manifests in type 2 inflammation at multiple sites (16), and in some nonatopic pulmonary diseases such as chronic obstructive pulmonary disease (9).

TSLP is a distant paralog of IL-7 and shares a common receptor subunit, IL-7Rα, with IL-7. TSLP binds the TSLP receptor (TSLPR) that is coupled with IL-7Rα to activate downstream pathways (17); TSLP-mediated signaling has been studied primarily in DCs and T lymphocytes, in which signaling occurred primarily through JAK/STAT pathways (18–20). A number of non-hematopoietic cell populations have been shown to express TSLPR and to be responsive to TSLP. Although the implications in allergic inflammation are not known, the barrier epithelium can respond to TSLP, and TSLP mediated recovery from colonic inflammation in a mouse model of colitis by inducing intestinal epithelial production of secretory leukocyte peptidase inhibitor (SLPI) (21). A growing body of literature also suggests that TSLP can activate a subset of sensory neurons to drive the itch response in allergic diseases such as AD (22, 23).

TSLPR is broadly expressed within hematopoietic cell populations (24). The highest expression is seen on specific myeloid DC populations (25–27), which have been shown to be important TSLP-responsive populations in both humans and mice. TSLP-stimulated DCs upregulated the costimulatory molecules CD40, CD80, CD86, and OX40L (28, 29). When cocultured with TSLP-conditioned DCs, naive syngeneic T cells proliferated but did not differentiate; naive allogeneic T cells cocultured with TSLP-conditioned DCs acquired an inflammatory Th2-like phenotype with production of IL-4, IL-5, IL-13, and TNF-α but not IL-10 (30). TSLP-conditioned DCs could also support the maintenance of Th2 effector memory cells and promotion of IgA2 class switching in the intestines (31, 32). The actions of TSLP directly on T cells can also promote type 2 responses. TSLP signaling on naive T cells in the presence of TCR stimulation promoted proliferation and Th2 differentiation through induction of IL-4 gene transcription (33–35). Recent data demonstrated that TSLP could directly promote Th2 differentiation and type 2 cytokine expression from naive T cells in vitro, even in the absence of IL-4 (18). In vivo, in an OVA/alum immunization model using antigen-specific T cells, it was noted that T cells lacking TSLPR acquired an effector phenotype after immunization but were defective in the ability to generate Th2 memory (36). In a variety of models of allergic disease, TSLP can regulate induction of Th2 cells and Th9 cells, likely through its effects on DCs and T cells (28, 29, 33–35, 37–40). TSLP can also act directly on Tregs in the skin and has been implicated in regulating the generation of Tregs in the thymus and microbiota-driven expansion and maintenance of Helios-negative Tregs in the gut (41–43). The impact of TSLP regulation of Tregs in allergic inflammation remains unclear.

In addition to DCs, basophils and innate lymphoid cells (ILCs) have also emerged as important innate effector cell populations downstream of TSLP. In mouse models, a TSLP/basophil axis has been shown to be important in experimental EoE and food allergy (44–46), and TSLP drove basophil hematopoiesis independent of IL-3 (47). In some models, TSLP-driven allergic inflammation was mediated by ILCs (48, 49). Given the importance of respiratory virus infections in driving asthma exacerbations, it is interesting to note that respiratory viruses can induce TSLP expression, and type I interferons induced during the antiviral response can play a counterregulatory role by modulating ILC2 activity (50–52). Several recent publications have now suggested that a TSLP/ILC axis may play a pivotal role in steroid-resistant allergic airway inflammation. TSLP signaling induced expression of the antiapoptotic protein BCL-XL in ILC2s and prevented corticosteroid-induced apoptosis of ILC2s in vitro (53). In vivo, TSLP signaling was not required to drive inflammation following OVA/IL-33 administration, but lack of TSLP signaling greatly enhanced the ability of dexamethasone to suppress inflammation in this model of allergic lung inflammation (53). Data from human subjects suggest a similar and important role for a TSLP/ILC axis, since TSLP could also mediate resistance to corticosteroids in ILC2s from human PBMCs and bronchoalveolar lavage (BAL) fluid. Furthermore, TSLP levels in the BAL fluid from asthmatic patients were inversely correlated with dexamethasone-mediated inhibition of IL-5 production from BAL fluid ILC2s (54). Since steroid therapy is a cornerstone for many allergic and inflammatory diseases, further study of the TSLP/ILC axis is certainly warranted to determine whether similar mechanisms regulate inflammation at other tissue sites.

IL-33

IL-33 is an IL-1 family cytokine that may exert a broad spectrum of effects extending from early immune development to atopic disease exacerbations. IL-33 was initially named "nuclear factor in high endothelial venules" (NF-HEV) based on its high expression in the nucleus of HEVs (55). The link between IL-33 and type 2 immune responses was established when IL-33 was identified as the ligand for suppression of tumorigenicity 2 (ST2; sometimes referred to as IL-1RL1, T1, or IL-33R) (56), which had been characterized previously as an orphan receptor important in type 2 responses in the lungs (57, 58). Genetic studies have reproducibly demonstrated significant associations between *IL33* and *IL1RL1* genetic variants and asthma in humans (59–66). Genetic variants in *IL1RL1* are also associated with AD risk (67), and genetic variants in the *IL33* and *IL1RL1* loci are associated with EoE risk (68, 69).

Epithelial cells at barrier surfaces and endothelial cells, both of which express IL-33 constitutively in the nucleus, are thought to be the primary sources of IL-33 during homeostatic and inflammatory conditions (67, 70, 71). A variety of other hematopoietic and non-hematopoietic cell types have also been reported to express IL-33 under basal conditions or after treatment with inflammatory

stimuli (67, 70, 72–79). In specific contexts, cell types other than epithelial and endothelial cells may serve as important sources for IL-33. For example, mast cell–derived IL-33 may be important in experimental autoimmune encephalitis and in intestinal helminth infections (80, 81).

Like the activity of other IL-1 family cytokines, the activity of IL-33 is regulated both by its localization within the cell and by proteolytic cleavage. IL-33 contains an N-terminal chromatin-binding motif and a predicted nuclear localization sequence. Although some studies suggest a role for IL-33 in transcriptional regulation (82), the intranuclear localization of IL-33 in most cell types is thought to be important in sequestering this cytokine to prevent inappropriate release (83). Transgenic mice that expressed a form of IL-33 that lacked the nuclear localization signal died of systemic inflammation (84). Although IL-33 lacks a signal sequence required for conventional secretory pathways, it can be released as an "alarmin" in response to cellular injury or stress (85, 86). Full-length IL-33 appears to be biologically active, but proteolytic cleavage of IL-33 at various sites can modulate its activity. Mast cell and neutrophil proteases can cleave and further activate IL-33 (87–89). Certain allergens also contain proteases that can cleave and further activate IL-33 (90). In contrast, cleavage of IL-33 by caspase-1, -3, or -7 or oxidation of IL-33 results in inactivation (91, 92). Splice variants of IL-33 also exist, although how these different isoforms differ in activity and regulation is not fully understood (93–95).

IL-33 binds a heteromeric receptor consisting of ST2 and its coreceptor IL-1 receptor accessory protein (IL-1RAcP). Formation of the IL-33/ST2/IL-1RAcP complex results in recruitment of MyD88 and IL-1R–associated kinase (IRAK) to activate a variety of downstream signaling pathways (96). A soluble variant of ST2 (sST2) that lacks the transmembrane domain appears to function as a decoy receptor to negatively regulate IL-33/ST2 signaling (97, 98). ST2 is constitutively expressed on several immune cell types, including mast cells, ILC2s, Th2 cells, and a subset of Tregs, and can be induced on many other immune subsets; as a consequence, IL-33 can also directly activate and induce cytokine production from a broad number of cell types (79, 99–109). Recently, leukotrienes and IL-33 have been shown to act together in a signaling circuit that may be an important amplifier of inflammation in allergic disease exacerbations. Signaling through the leukotriene receptor CysLT2R on alveolar cells drove the production of IL-33, which acted on T cells to upregulate T cell expression of the leukotriene receptor CysLT1R (110, 111). Some non-hematopoietic cell types are also IL-33–responsive. ST2 expressed on human airway epithelium may mediate inflammatory cytokine production from the bronchial epithelium (112, 113); and, like TSLP, IL-33 has also been shown to mediate the itch response through activation of sensory neurons (114).

IL-33 is a particularly potent activator of ILC2s, which produce type 2 cytokines such as IL-13 and IL-5 and upregulate surface OX40L and PD-L1 in response to IL-33 (107, 115–118). In mice, systemic IL-33 also mobilized ILC2 precursors from the bone marrow (119). In a papain-driven model of allergic lung inflammation, IL-33–mediated activation of ILC2s was important in inducing Th2 cells in the draining lymph nodes and in promoting memory Th2 responses in the lungs (120, 121). Memory Th2 cells, which express ST2 at higher levels than effector Th2 cells, are another important effector cell type responsive to IL-33 (122, 123). In vivo, after house dust mite (HDM) exposure, IL-33 signaling on memory Th2 cells induced amphiregulin production, which then drove osteopontin production by eosinophils (123, 124). It is interesting to note that EGFR, the receptor for amphiregulin, can form a complex with ST2, and EGFR was required for IL-33–induced IL-13 production during helminth infections in mice (125). In helminth infection, an $ST2^+$ subset of memory Th2 cells was required to drive production of major basic protein (MBP) by eosinophils after infection (123, 124). While ILC2 and pathogenic memory Th2 cell populations both express high levels of ST2 and share transcriptional and epigenetic profiles (126), Th2 cells but not ILC2s express DUSP10, a phosphatase that can negatively regulate IL-33–mediated cytokine production (127). It is now also clear that IL-33 can promote the induction and function of Tregs in a variety of settings (103, 128–130). The implications of this role for IL-33 in suppressing inflammation in allergic disease are not fully understood, though IL-33 was shown to negatively regulate allergic inflammation by inducing Tregs via an IL-33/mast cell/IL-2 axis (131).

In the developing lungs in mice, IL-33 has been shown to have an important role in establishing the pulmonary immune environment that influences the risk and development of allergic lung inflammation later in life. These studies have shown direct links between perturbations in IL-33/ST2 signaling in the perinatal period and subsequent type 2 responses to allergen. Following a perinatal increase in IL-33 expression in the lungs, pulmonary ILC2 frequencies increased (132–134). ILC2s mediated eosinophil accumulation in the lungs during the neonatal period and were the primary source of IL-13 in the neonatal lungs that drove the phenotypic polarization of pulmonary macrophages. Tissue insults such as hyperoxia that occur during the perinatal period can increase IL-33 expression and mobilize ILC2s, leading to increased susceptibility to asthma later in life (135). IL-33 also drove a lung-specific transcriptional program in basophils in the developing lungs, since the gene expression profile of lung basophils from ST2-deficient neonatal mice was more similar to that of wild-type circulating basophils than to that of wild-type lung basophils (136). Thus, IL-33 signaling impacts all stages of allergy starting even from the establishment of the immune environment in the perinatal lungs.

IL-25

IL-25 (sometimes referred to as IL-17E) is a member of the IL-17 cytokine family, although the functions of IL-25 have been shown to be quite distinct from those of other IL-17 cytokine family members given IL-25's ability to amplify type 2 inflammation at multiple tissue sites (137–140). Blockade of IL-25 signaling can attenuate allergic inflammation in a variety of mouse models (141–143). Although initial reports described IL-25 as a Th2 cell–derived cytokine (137), epithelial cells, alveolar macrophages, mast cells, basophils, and eosinophils have now also been reported as potential sources of IL-25 (141, 144–148). IL-25 was constitutively expressed by epithelial cells of the skin and lungs in subjects with asthma or atopic disease, and expression of IL-25 was higher in the skin and lungs of subjects with asthma and atopic disease than in the skin and lungs of control subjects (147, 148). In subjects with chronic

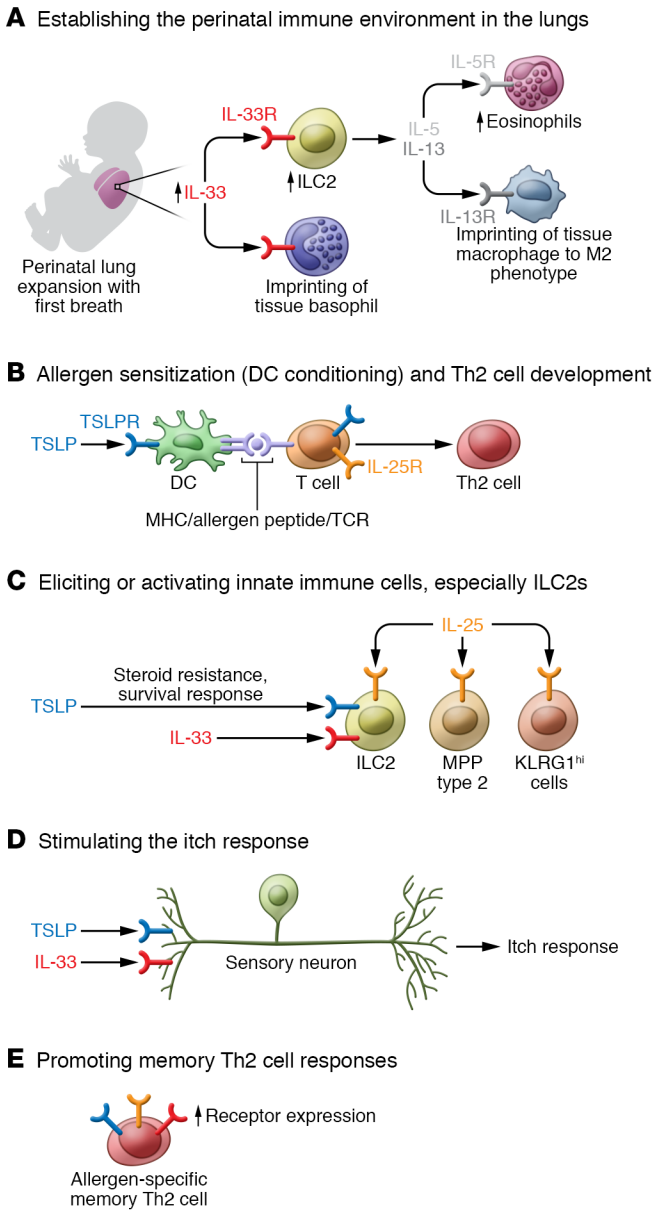

Figure 1. TSLP, IL-33, and IL-25 regulate a diversity of responses in type 2 immunity. (**A**) IL-33 release in the lungs at birth helps establish the pulmonary immune environment, which can influence asthma risk and development later in life. (**B**) TSLP acts directly on DCs to drive Th2 cell development; IL-25, along with IL-4, can also drive Th2 cell differentiation. (**C**) TSLP, IL-33, and IL-25 act on a broad array of innate immune cells and are particularly important in eliciting and activating ILC2s; IL-25 can also elicit MPP type 2 cells and IL-17^{+} KLRG1^{hi} cells. (**D**) TSLP and IL-33 can act on sensory neurons to stimulate the itch response. (**E**) TSLP, IL-33, and IL-25 can promote adaptive type 2 responses through subsets of memory Th2 cells that are characterized by high receptor expression for TSLP, IL-33, and IL-25.

rhinosinusitis, solitary chemosensory cells (SCCs) appeared to be the primary source of IL-25 within the sinonasal epithelium, and SCCs were expanded in nasal polyp tissue compared with adjacent turbinate epithelium (149). Within the lungs and intestines in mice, IL-25 expression was restricted to tuft cells, a rare type of chemosensory epithelial cell (150–152). IL-25 expression by tuft cells was further induced by succinate or helminth-derived products and mediated intestinal epithelial remodeling in response to colonizing protozoa, which protected against helminth infections (150, 153, 154). Few data exist on whether IL-25 expression and function are regulated by splicing or proteolytic cleavage; however, IL-25 has been reported to be a substrate for cleavage by matrix metalloproteinase 7 (MMP-7) (155).

IL-25 binds IL-17RB, and along with IL-17RA recruits the adapter protein Akt1 to activate downstream signaling pathways (138, 156–159). Cellular targets of IL-25 include T cells, ILC2s, specific myeloid populations, and invariant NKT cells, as well as non-hematopoietic cell populations such as fibroblasts, epithelial cells, endothelial cells, and mesenchymal cells (118, 137, 146, 147, 160–166). An IL-25–responsive, steroid-resistant myeloid population was a critical mediator of disease in a model of cockroach allergen–driven chronic allergic lung inflammation (167). In addition to acting on ILC2s, which are activated or elicited by TSLP and IL-33, IL-25 may also induce some functionally and phenotypically distinct ILC populations: multipotent progenitor (MPP) type 2 cells and IL-17–producing KLRG1^{hi} cells (162, 165). A subset of NKT cells has also been shown to produce type 2 cytokines in response to IL-25 and could drive airway hyperresponsiveness in an OVA/alum model of allergic airway inflammation (164). As with TSLP and IL-33, T cells also appear to be important target cells in IL-25–mediated inflammation. Ex vivo analyses of human peripheral blood demonstrated high expression of IL-17RB transcript and protein in memory Th2 cells that was greatly enhanced by coculture with TSLP-conditioned DCs (147). Augmentation of Th2 differentiation and function by IL-25 appeared to be dependent on IL-4, since naive T cells lacking IL-4 or antibody blockade of IL-4 abrogated the ability of IL-25 to induce Th2 differentiation in vitro (146). IL-25 does not appear to drive Th9 differentiation, but Th9 cells expressed IL-17RB and increased IL-9 production in response to IL-25 (168). Under homeostatic conditions, IL-25 can play an important role in limiting IL-17 expression within the gut. Intestinal commensal microbiota drove expression of IL-25 from the epithelium, which limited IL-23 expression and Th17 cell expansion in the large intestines and limited IL-22 production from RORγt^{+} ILCs (ILC3s) in the small intestines (169, 170). Although the implications in allergy are unclear, recent data also demonstrated an important role for IL-25 in driving keratinocyte proliferation and skin inflammation in an IL-17–dependent imiquimod-induced psoriasis model (171). Additional data linking IL-25 to Th17-type responses come from a hapten-mediated model of contact hypersensitivity (CHS). CHS mediated by transferred Th2 cells was comparable in wild-type and IL-25–deficient mice, yet transferred Th17 cells could drive inflammation in wild-type but not IL-25–deficient mice (172).

TSLP, IL-33, and IL-25: interplay and tissue-specific roles

Although TSLP, IL-33, and IL-25 can all promote type 2 inflammation through their effects on a broad array of cell populations (Figure 1 and Table 1), the downstream effector profiles can be distinct in response to these three cytokines (173), and cells may express different levels of receptors for TSLP, IL-33, or IL-25 in a tissue-dependent manner (174). Studies in mouse models have demonstrated

Table 1. Cellular sources and targets of TSLP, IL-33, and IL-25

	TSLP	IL-33	IL-25
Sources			
Non-hematopoietic	Epithelial cells	Epithelial cells	Epithelial cells (esp. tuft cells, solitary chemosensory cells)
	Stromal cells	Endothelial cells	
		Fibroblastic reticular cells, fibroblasts, fibroblast-like cells, myofibroblasts	
		Adipocytes	
		Smooth muscle cells	
		Glial cells	
		Hepatocytes	
Hematopoietic	Dendritic cells	Various myeloid cell types	Alveolar macrophages
	Mast cells	Mast cells	Mast cells
	Basophils	Platelets, megakaryocytes	Basophils
			Eosinophils
			Th2 cells
Targets			
Non-hematopoietic	Epithelial cells	Epithelial cells	Epithelial cells
	Sensory neurons	Endothelial cells	Endothelial cells
		Stromal cells, fibroblasts	Fibroblasts
		Sensory neurons	Mesenchymal cells
		Glial cells	
		Cardiomyocytes	
Hematopoietic	Type 2 ILCs (ILC2s)	Type 2 ILCs (ILC2s)	Type 2 ILCs
	$CD4^+$ T cells	$CD4^+$ T cells	(ILC2s, MPP type 2, IL-17^+KLRG1^{hi})
	(Th2, Th9, naive T cells)	(Th2, Th1, Th17)	$CD4^+$ T cells (Th2, Th9, naive T cells)
	Tregs	Tregs	iNKT cells
	$CD8^+$ T cells	$CD8^+$ T cells	Specific myeloid populations
	NKT cells	NK cells	
	B cells	iNKT cells	
	Mast cells	B cells	
	Basophils	Mast cells	
	Eosinophils	Basophils	
	Dendritic cells	Eosinophils	
	Monocytes, macrophages	Dendritic cells	
		Macrophages	
		Neutrophils	

differential requirements for TSLP, IL-33, and IL-25. In some models, the allergen dose or mouse genetic background can influence the requirements for these epithelial cell–derived cytokines. At low doses of HDM, blockade of either IL-33 or GM-CSF but not TSLP attenuated HDM-driven allergic lung inflammation, but inflammation driven by high-dose HDM was attenuated in the absence of TSLP signaling (175). C57BL/6 mice that lacked TSLP signaling had greatly attenuated skin inflammation after topical application of the vitamin D analog MC903 (48); yet, in BALB/c mice, IL-25 may play a more important role than TSLP, since MC903-driven inflammation was decreased to a greater extent in mice that lacked the IL-25 receptor IL-17RB than in mice that lacked either TSLPR or ST2 (117). Some studies suggest a tissue-specific role for TSLP, IL-33, and IL-25, as mice lacking TSLP, IL-33, and IL-25 signaling had impaired type 2 immune responses in tissue in helminth infection or after HDM challenge despite the fact that lymph node priming of adaptive type 2 immunity remained intact (126).

The recent identification of subsets of memory Th2 cells in humans and mice that are characterized by high expression of receptors for TSLP, IL-33, and IL-25 supports a role for these three cytokines in regulating adaptive immune responses in allergy. These Th2 subpopulations are enriched at affected sites in EoE and AD and constitute a higher frequency of circulating Th2 cells in subjects with seasonal allergies than in control subjects (176, 177). It is interesting to speculate whether the increased responsiveness of these memory Th2 cells to TSLP, IL-33, and IL-25 may be important in mediating the allergic phenotype, since the mere presence or absence of allergen-specific T cells does not appear to distinguish allergic from nonallergic subjects (178, 179). Additional research is required to assess whether each of these epithelial cell–derived cytokines is uniformly required across a spectrum of human allergic diseases or whether patterns of expression of these cytokines may distinguish distinct allergic endotypes or phenotypes.

Other epithelial cytokines

While TSLP, IL-33, and IL-25 have been highlighted as important epithelial cell–derived cytokines in allergy because of their potent ability to drive type 2 responses, it is important to note that numerous other cytokines produced by the barrier epithelium also have key roles in regulating allergic diseases. A growing body of literature implicates granulocyte-macrophage colony-stimulating factor (GM-CSF) in the regulation of allergic responses. GM-CSF was able to serve as an adjuvant to drive type 2 lung inflammation in response to low-dose HDM or OVA alone (180, 181), and blockade or loss of GM-CSF signaling attenuated allergic inflammation in a variety of mouse models (175, 182–185). Studies examining the role of GM-CSF in allergic lung inflammation suggest a primary role for GM-CSF during allergic sensitization (184). IL-1α may also be important during sensitization but not challenge since neutralization of IL-1α but not IL-1β during sensitization reduced type 2 inflammation in an HDM-driven asthma model, whereas inflammation was not affected by blockade of IL-1α or IL-1β during the challenge phase in this model (175). In fact, TLR4-induced IL-1α from bronchial epithelial cells provided an important autocrine signal for GM-CSF and IL-33 release, suggesting that IL-1α may be one of the earliest triggers of type 2 immunity in the lungs. Studies of AD also suggest that keratinocyte release of IL-1α can drive chronic skin inflammation (186).

Table 2. Clinical trials of drugs targeting TSLP or IL-33/ST2[A]

Study title	Clinical trial identifier	Stage	Drug	Condition/disease
Anti-TSLP clinical trials				
Safety Study of AMG 157 in Healthy Subjects	NCT00972179	Phase I	Tezepelumab	Healthy
A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Immunogenicity of MEDI9929 After Single Administration in Healthy Male Japanese Subjects	NCT01913028	Phase I	Tezepelumab	Healthy
A Study to Evaluate the Pharmacokinetics of MEDI9929 (AMG 157) in Adolescents with Mild to Moderate Asthma	NCT02512900	Phase I	Tezepelumab	Asthma
Double-blind, Multiple Dose Study in Subjects with Mild Atopic Asthma	NCT01405963	Phase I	Tezepelumab	Asthma
Safety Study of AMG 157 in Healthy Subjects and Subjects with Atopic Dermatitis	NCT00757042	Phase I	Tezepelumab	Healthy, atopic dermatitis
Anti-TSLP (AMG 157) Plus Antigen-Specific Immunotherapy for Induction of Tolerance in Individuals with Cat Allergy	NCT02237196	Phase I/phase II	Tezepelumab	Cat allergy/ hypersensitivity
Study to Evaluate the Efficacy and Safety of MEDI9929 (AMG 157) in Adult Subjects with Inadequately Controlled, Severe Asthma	NCT02054130	Phase II	Tezepelumab	Asthma (191)
Effects of Anti-TSLP in Patients with Asthma (UPSTREAM)	NCT02698501	Phase II	Tezepelumab	Asthma
Study to Evaluate Tezepelumab on Airway Inflammation in Adults with Uncontrolled Asthma (CASCADE)	NCT03688074	Phase II	Tezepelumab	Asthma
Phase 2a Study to Evaluate the Efficacy and Safety of MEDI9929 in Adults with Atopic Dermatitis (ALLEVIAD)	NCT02525094	Phase II	Tezepelumab	Atopic dermatitis (194)
Study to Evaluate Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (NAVIGATOR)	NCT03347279	Phase III	Tezepelumab	Asthma
Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma	NCT03706079	Phase III	Tezepelumab	Asthma
Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma	NCT03406078	Phase III	Tezepelumab	Asthma
Anti–IL-33/ST2 clinical trials				
Proof of Concept Study to Investigate ANB020 Activity in Adult Patients with Severe Eosinophilic Asthma	NCT03469934	Phase II	Etokimab	Asthma
A Study Investigating the Efficacy, Safety, and PK Profile of ANB020 Administered to Adult Subjects with Moderate-to-Severe AD	NCT03533751	Phase II	Etokimab	Atopic dermatitis
Placebo-Controlled Study to Investigate ANB020 Activity in Adult Patients with Peanut Allergy	NCT02920021	Phase II	Etokimab	Peanut allergy
Etokimab in Adult Patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)	NCT03614923	Phase II	Etokimab	Chronic rhinosinusitis with nasal polyps
A First-in-Human, Double Blind, Single Dose Study in Healthy Subjects and Subjects With Mild Atopic Asthma	NCT01928368	Phase I	AMG 282	Asthma
A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 282 in Healthy Subjects and Subjects With Chronic Rhinosinusitis with Nasal Polyps	NCT02170337	Phase I	AMG 282	Chronic rhinosinusitis with nasal polyps
Safety and Tolerability of MEDI3506 in Healthy Subjects, in Subjects With COPD and Healthy Japanese Subjects	NCT03096795	Phase I	MEDI3506	Chronic obstructive pulmonary disease
Proof-of-Concept Study to Assess the Efficacy, Safety and Tolerability of SAR440340 (Anti-IL-33 mAb) in Patients With Moderate-to-Severe Chronic Obstructive Pulmonary Disease (COPD)	NCT03546907	Phase II	SAR440340	Chronic obstructive pulmonary disease
Efficacy and Safety Study of GSK3772847 in Subjects With Moderately Severe Asthma	NCT03207243	Phase II	GSK3772847	Asthma
Repeat Dose Study of GSK3772847 in Participants With Moderate to Severe Asthma With Allergic Fungal Airway Disease (AFAD)	NCT03393806	Phase II	GSK3772847	Asthma with allergic fungal airway disease
Anti-ST2 (MSTT1041A) in COPD (COPD-ST2OP)	NCT03615040	Phase II	MSTT1041A	Chronic obstructive pulmonary disease

[A]From ClinicalTrials.gov, accessed December 5, 2018. Includes trials that are completed or recruiting.

Studies have also highlighted a potential role for TGF-β, and, in particular, epithelial cell–derived TGF-β, in the pathogenesis of asthma. A critical role for TGF-β in mediating tolerance through Treg induction has been well established; thus, some studies have investigated TGF-β in allergy as a potential mode of therapy (187, 188). However, loss of TGF-β expression specifically from the bronchial epithelium reduced ILC2 accumulation and IL-13 production in the lungs following HDM administration (189). The association of SNPs in the promoter and coding regions of the *TGFB1* gene with asthma susceptibility and degree of atopy further supports an important role for TGF-β in allergic disease (190). Given the opposing roles that have been described for

TGF-β in suppressing or promoting allergic inflammation, further study is needed to better understand how TGF-β regulates type 2 immunity at barrier tissue sites.

Development of biologics against epithelial cytokines

Although biological therapies directed against IgE and some effector cytokines have been developed, studies in mouse models suggest that epithelial cell–derived cytokines such as TSLP, IL-33, and IL-25 may regulate allergic responses more broadly and through more diverse pathways than IgE or type 2 effector cytokines such as IL-4, IL-13, or IL-5. There is therefore growing interest in developing therapeutics to target TSLP, IL-33, and IL-25. Antibodies directed against IL-25 are under development but have not yet entered clinical trials. One antibody directed against TSLP and several antibodies that block IL-33/ST2 signaling are under development (Table 2). Therapeutics directed against TSLP and IL-33 have not yet been approved by the FDA, but several trials that have been conducted suggest that these antibodies may be both safe and effective in a variety of atopic diseases.

TSLP signaling blockade. Tezepelumab (AMG 157/MEDI9929) is a human IgG2 monoclonal antibody that binds human TSLP and prevents the binding of TSLP with TSLPR. Tezepelumab was effective in reducing rates of asthma exacerbations in patients with moderate to severe disease requiring long-acting β-agonists and medium to high doses of inhaled glucocorticoids (191). A study of responses to allergen challenge in patients with mild allergic asthma suggested that tezepelumab affects both early and late asthmatic responses to allergen exposure (192). Treatment with tezepelumab did not affect total IgE levels in patients with mild asthma but did decrease blood eosinophil counts compared with those of placebo-treated control subjects. Allergen-induced bronchoconstriction after allergen challenge was also attenuated in tezepelumab-treated patients compared with controls. Studies are currently ongoing to evaluate the efficacy of tezepelumab as adjunctive therapy to immunotherapy in inducing long-term tolerance to cat allergen (193). ALLEVIAD, a phase IIa study of safety and efficacy of tezepelumab in adults with AD, has also been completed, and although higher numbers of subjects treated with tezepelumab reached an improvement of 50% or more in the Eczema Area Severity Index (EASI-50), the study did not reach the level of significance in this primary endpoint (194). It will be particularly interesting to establish whether blockade of TSLP may be effective in steroid-resistant asthma given recent studies suggesting a central role for TSLP and ILCs in steroid resistance in mouse models of allergic inflammation.

IL-33 signaling blockade. Etokimab (ANB020) is a humanized anti–IL-33 IgG1 antibody generated by AnaptysBio that is being evaluated in a number of studies in the treatment of AD, eosinophilic asthma, peanut allergy, and chronic rhinosinusitis with nasal polyps (195). In vitro analyses demonstrated high-affinity binding to IL-33 and inhibition of IL-33 activity on primary human cells. Phase I and phase IIa trials of etokimab have been completed. Etokimab demonstrated a favorable safety profile, and a single dose of etokimab suppressed IL-33 function for 85 days based on ex vivo assays. In adult subjects with AD that was inadequately controlled with topical corticosteroids, single dosing was also able to achieve an improvement of 50% or more in the EASI-50 eczema grading index (196). Interim analyses of a phase IIa study of etokimab in adults with severe eosinophilic asthma demonstrated improvements in forced expiratory volume (FEV1) at day 2 in etokimab-treated patients over patients receiving placebo, and differences in FEV1 measurements between etokimab-treated and placebo-treated patients remained significant at day 64 (197). Improvements in lung function also correlated with reductions in blood eosinophil numbers. Positive responses have also been reported in interim analyses of a phase IIa trial of etokimab in adult peanut allergy patients with a clinical history of anaphylaxis (198).

Conclusions

Substantial progress has been made in understanding the mechanisms that underlie the development and progression of allergic diseases. The regulation of barrier tissue immune homeostasis by TSLP, IL-33, and IL-25 affects susceptibility to allergic disease development but also modulates the function of cell populations such as memory Th2 cells and ILCs that drive allergic disease exacerbations. Thus, biologics directed against these epithelial cell–derived cytokines may be effective across a broad spectrum of allergic diseases. Antibodies against IL-25 are still in the early stages of development. The anti-TSLP antibody tezepelumab and the anti–IL-33 antibody etokimab have now shown promising results in a variety of allergic diseases. Ongoing and future studies will help establish whether biologics targeting TSLP, IL-33, or IL-25 can offer safe, effective, and steroid-sparing treatments for allergy.

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