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Thymic stromal lymphopoietin (TSLP) and allergic disease

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Abstract

The importance of the epithelium in initiating and controlling immune responses is becoming more appreciated. For example, allergens contact first occurs at mucosal sites in exposed to the external environment such as the skin, airways and gastrointestinal tract. This exposure leads to the production of a variety of cytokines and chemokines that are involved in driving allergic inflammatory responses. One such product is thymic stromal lymphopoietin (TSLP). Recent studies, in both humans and mouse models, have implicated TSLP in the development and progression of allergic diseases. This review will highlight recent advances in the understanding of the role of TSLP in these inflammatory diseases. Importantly, these insights into TSLP's multifaceted roles could potentially allow for novel therapeutic manipulations of these disorders.

Keywords

TSLP; asthma; allergy; atopic dermatitis; inflammation

Introduction

The atopic diseases consist of the triad of asthma, allergic rhinitis, and atopic dermatitis. These diseases share a common pathogenesis, involving inflammatory Th2-type cytokines and elevated IgE. Interestingly, they frequently present together in the same individual and family, suggesting common factors and mechanisms are involved in these diseases. Recent evidence has been accumulated to suggest that Th2-type CD4⁺ T cells play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, i.e. the cellular triad involved in the allergic inflammation. However, the mechanisms underlying the preferential activation by environmental allergens of Th2 cells in atopic individuals still remain obscure.

One likely candidate for a factor involved in the initiation of allergic inflammatory responses is the cytokine thymic stromal lymphopoietin (TSLP). TSLP is expressed by epithelial cells, with the highest levels seen in lung and skin-derived epithelial cells⁽¹⁾. Studies using both human and mouse CD11c⁺ dendritic cells showed that these cells produced CCL17 and CCL22, chemokines capable of attracting Th2-type CD4⁺ T cells, following exposure to TSLP^(1;2). In addition, when naïve CD4⁺ T cells are primed on TSLP-

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treated DCs they take on an inflammatory Th2 phenotype, producing IL-4, IL-5, IL-13, and TNF- α upon restimulation⁽²⁾. It has recently been shown that TSLP is also a potent growth and survival factor for Th2 effector cells⁽³⁾. Notably, a relationship between expression of TSLP and the presence of the atopic diseases asthma, atopic dermatitis, and allergic rhinitis has been established^(2;4;5). Taken as a whole, these data provide strong evidence of a link between TSLP and the initiation and progression of allergic inflammatory disease. This hypothesis is currently being tested clinically as a humanized monoclonal antibody against TSLP is in the clinic, with asthma as the primary indication, and has successfully completed Phase I studies.

TSLP Biology

Thymic stromal lymphopoietin (TSLP) is a member of the 4-helix bundle cytokine family, and a distant paralog of IL-7⁽⁶⁾. Murine TSLP was discovered as an activity in the supernatants of a thymic stromal cell line capable of supporting immature B cell proliferation and development^(7;8). Consistent with its similarity to IL-7, TSLP was shown to co-stimulate thymocyte proliferation and to promote B cell lymphopoiesis^(9;10). Subsequently a human homolog was identified using *in silico* methods⁽¹¹⁾. Interestingly, human and murine TSLP share modest sequence homology (~45% at the nucleotide and amino acid level) but a significant degree of functional homology^(1;10).

Several groups identified a cell-surface receptor capable of binding TSLP with low affinity (TSLPR subunit), which shares 24% identity to the common γ_c receptor chain (γ_c)^(12;13). The functional receptor (TSLPR) was shown to include both the TSLPR subunit and the IL-7R α chain in both humans and mice (Fig. 1)^(11;13). The functional TSLPR is expressed by a variety of hematopoietic cell populations, including T cells, B cells, NKT cells, monocyte/macrophages, basophils, and dendritic cells (DCs), as well as some non-hematopoietic cell lineages such as epithelial cells^(14;15). While classified as a hematopoietin receptor based on structural homology, the TSLPR subunit contains notable differences from canonical hematopoietin receptors. These include a modified WSXWS motif and lack of a Box2 motif (involved in Janus kinase [JAK] binding)^(13;16).

Little is known as to the signaling pathways that are activated following engagement of the TSLP receptor complex. Initial studies in the mouse showed that signal transducers and activators of transcription (STAT)5 was activated, but in the absence of detectable JAK activation⁽⁹⁾, making TSLPR unique among members of the hematopoietic receptor family. However, two recent papers have demonstrated robust and sustained activation of JAK-1 and -2 following TSLP signaling in primary human dendritic cells and primary human and mouse CD4⁺ T cells^(17;18). Surprisingly, unlike IL-7R α and γ_c in IL-7 signaling, which utilize JAK-1 and -3, the TSLPR subunit bound and utilized JAK-2 in concert with IL-7R α -associated JAK-1. These latest findings resolve a long-standing question about the mode of TSLP signaling, and show that TSLP-induced JAK activation precedes the activation of STAT proteins. In the human, recent studies have shown that, in addition to STAT5, TSLP stimulation activated STAT 1,3,4,5, and 6, as well as JAKs 1 and 2⁽¹⁷⁾. One possible explanation for the discrepancy in the data between species is that the mouse signaling work used a pre-B cell line, while the human studies were in primary dendritic cells. Consistent with this explanation, our lab has shown that TSLP-treated mouse DCs activate Jak1 and Jak2, as well as STATs 1, 3, and 5 (Bell, Kitajima, Larson, Sakamoto, Wagner, Reizis, Hennighausen, and Ziegler, manuscript submitted). These data suggest that TSLP is capable of activating multiple STAT proteins. Whether TSLP utilizes similar signaling pathways in other cell lineages and how each STAT molecule contributes has yet to be elucidated.

As mentioned above, several cell types have been shown to respond to TSLP. TSLP was originally isolated and characterized as a lymphocyte growth factor^(8–10), and subsequent studies have shown that TSLP can promote T cell proliferation and differentiation both *in vivo* and *in vitro*^(3;19;20). Finally, as will be detailed below, TSLP responsiveness of CD4 T cells is a critical feature of the challenge phase of allergic inflammation^(21;22).

It has now become apparent that a major TSLP-responsive cellular subset in both humans and mice are myeloid-derived dendritic cells (mDCs)^(1;23). Co-culture of TSLP-activated DCs with naïve syngeneic CD4⁺ T cells led to T cell proliferation but no differentiation, suggesting a role for TSLP in CD4⁺ T cell homeostasis⁽²⁴⁾. However, when TSLP-stimulated DCs primed CD4⁺ T cells in an antigen-specific manner (e.g., in an allogeneic culture), the resulting T cells display characteristic features of Th2 differentiated cells (production of IL-4, IL-5, IL-13, and TNF α), with the exception that IL-10 production was not evident⁽²⁾. These data suggest that TSLP-activated DCs primed for inflammatory Th2 cell differentiation. Interestingly, TSLP, in the absence of IL-12, induced OX40L expression on DCs, and OX40-OX40L interactions were critical for the ability of the DCs to drive Th2 cell differentiation⁽²⁵⁾. Consistent with a role in regulating Th2 cytokine responses, TSLP-activated DCs were also capable of supporting the maintenance and further polarization of CRTH2⁺ Th2 effector memory cells⁽²⁶⁾. TSLP-conditioned DCs also augmented intestinal epithelial cell-mediated IgA2 class switching through the induction of APRIL⁽²¹⁾. Finally, some *in vitro* studies have suggested a role for TSLP in the generation of tolerogenic DCs that can drive the differentiation of regulatory T cells (Tregs)^(27–29), although other studies have indicated that TSLP may hinder the production and/or maintenance of FOXP3⁺ Tregs *in vivo* in certain disease processes⁽³⁰⁾.

Finally, several innate immune cells express the TSLPR and respond to TSLP. For example, TSLP can enhance cytokine production from mast cells, NKT cells and eosinophils^(31–33). Recent work has highlighted direct effects of TSLP on basophils during TH2 cytokine-associated inflammatory diseases, including promotion of basophil hematopoiesis from the bone marrow in an IL-3-independent manner⁽³⁴⁾.

Taken as a whole, the plethora of cell types that can respond to TSLP demonstrate the important role of this cytokine in orchestrating the initial response to an epithelial insult (Figure 2). While the normal function of TSLP is likely the maintenance of Th2-type homeostasis at barrier surfaces⁽¹⁴⁾, as will be described in the next section, dysregulated TSLP expression can result in the development of type 2 inflammatory responses leading to allergic disease.

TSLP and allergic diseases

The first link of TSLP to allergic disease came from studies by Soumelis and colleagues showing elevated expression of TSLP in the lesional skin of atopic dermatitis patients⁽²⁾. Since then numerous studies in both humans and mice have implicated TSLP in other atopic diseases, including asthma, allergic rhinitis and food allergies^(4;5;35). The following sections describe the disorders associated with TSLP and what is known about the mechanisms through which TSLP may act.

Atopic Dermatitis—Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects an estimated 10 to 20 percent of infants and young children in the United States⁽³⁶⁾. While no single nucleotide polymorphisms (SNPs) in or around the TSLP gene locus have yet been associated with AD⁽³⁷⁾, TSLP was highly expressed in acute and chronic AD lesions⁽²⁾. Interestingly, cytokines that are found at high levels in lesional skin in these patients (IL-1 β , TNF α , IL-4 and IL-13) can also synergize to induce TSLP expression by keratinocytes⁽³⁸⁾, suggesting a feed-forward inflammatory cascade. Consistent with a role in

initiating allergic inflammation in the skin, Corrigan et al⁽³⁹⁾ found that TSLP was rapidly induced following cutaneous allergen challenge, leading to the recruitment and subsequent activation of DCs.

More recently, it was shown that patients with Netherton syndrome (NS), a severe ichthyosis in which affected individuals experience a significant predisposition for atopic disease⁽⁴⁰⁾, have elevated levels of TSLP in their skin⁽⁴¹⁾. NS is caused by mutations in the serine protease inhibitor Kazal-type 5 (*SPINK5*) gene, which encodes the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI)⁽⁴²⁾. LEKTI deficiency leads to dysregulation of the protease kallikrein 5, which in turn activates protease-activated receptor-2 (PAR-2). Activated PAR-2 has been shown to induce the expression of TSLP from either keratinocytes or airway epithelial cells^(41;43). In *SPINK5* knockout (*SPINK5* $-/-$) mice, which reproduce many of the key features of NS, the absence of LEKTI resulted in unrestrained activity of the serine protease kallikrein 5, which directly activated proteinase-activated receptor 2 (PAR-2) and induced nuclear factor κ B (NF- κ B)-mediated overexpression of TSLP^(41;43). Thus, a mutation that increases TSLP expression in the skin has direct consequences on the development of a severe atopic disease in both humans and mice.

In mice, over-expression of TSLP in the skin was sufficient to induce a disease phenotype characterized by all of the hallmark features of AD⁽⁴⁴⁾. These features included marked thickening of the epidermis, infiltration of the dermis with inflammatory leukocytes and the presence of Th2 cells in skin-draining lymph nodes and the production of type-2 cytokines in skin. Similarly, an antigen driven model of dermatitis that also uses barrier disruption via tape-stripping, He et al.⁽²¹⁾ found that TSLP signaling was required for development of skin inflammation.

Targeted deletion of specific genes in keratinocytes has also been used to study the regulation of TSLP-mediated inflammation. For example, keratinocyte-specific ablation of the retinoid X receptor isotypes RXR α and RXR β resulted in upregulation of TSLP and development of AD-like skin inflammation⁽⁴⁵⁾. The mechanism that underlies this phenotype is unclear, but the results suggest that RXRs are involved in the regulation of TSLP gene expression. Consistent with this model was the finding that treatment of airway epithelial cells with an RXR agonist down-regulated TSLP expression through inhibition of NF κ B signaling⁽⁴⁶⁾. Activation of nuclear hormone receptors can also induce TSLP expression. For example, administration of vitamin D or its analogs upregulated TSLP and resulted in the development of dermatitis⁽⁴⁷⁾, suggesting that vitamin D administration may result in RXR derepression and recruitment of co-activators to promote transcription.

Keratinocyte-specific deletion of total Notch signaling, which causes severe epidermal differentiation defects, also resulted in high systemic levels of TSLP and type-2 skin inflammation^(48;49). However, TSLP expression in this model may be due to responses to the resulting skin barrier defect rather than directly from the loss of keratinocyte-specific Notch signaling itself, since wild-type and mutant keratinocytes produced similar amounts of TSLP in *in vitro* cultures⁽⁴⁹⁾.

The role of TSLP in fluorescein isothiocyanate (FITC)-mediated contact hypersensitivity, a Th2-mediated model of human allergic contact dermatitis, has recently been elucidated. TSLP expression is induced following priming with FITC. The induction of TSLP gene expression is mediated by a component of the solvent used to dissolve the FITC, dibutyl phthalate⁽⁵⁰⁻⁵²⁾. TSLPR-deficient mice failed to mount a response following challenge, as did mice where TSLP was neutralized during both priming and challenge⁽⁵⁰⁾. Blockade of TSLP during challenge alone partially reduced the response, suggesting that TSLP is

required at both priming and challenge to generate a complete response⁽⁵²⁾. Unlike the tape-stripping model, in this system a defect was found in skin resident dendritic cells in TSLPR-deficient mice. Antigenbearing dendritic cells from TSLPR^{-/-} mice displayed a migration defect as well as a reduced capacity to drive CD4 T cell proliferation⁽⁵⁰⁾. TSLPR-deficient CD4 T cells were indistinguishable from their wild-type counterparts in their ability to proliferate and infiltrate the skin following FITC sensitization (SFZ and RP Larson, manuscript in preparation). These data are consistent with TSLP driving CD4 T cell proliferation indirectly, possibly via activated dendritic cells.

Two important unanswered questions concerning the role of TSLP in allergic inflammation is during which phase of the response does it exert its influence, and on which cell types. For example, TSLP has been shown to be involved in both the initiation and progression of allergic skin inflammation, but the relative contribution to these stages and the cellular requirements may differ depending on the context. Langerhans cell (LC) migration and activation was seen in human AD lesions *in situ*⁽²⁾. Furthermore, TSLP has been shown to increase the number and maturation status of migratory LCs in human skin explants cultures and to condition LCs to prime co-cultured naïve CD4⁺ T cells to adopt an inflammatory TH2 phenotype⁽⁵³⁾. The data in mouse models of AD implicate TSLP in both sensitization and challenge, but that different cell types appear to be important as targets at each phase. Using a model of hapten-mediated contact hypersensitivity, Larson *et al.* showed that TSLP is important during sensitization, acting on skin-resident DCs to drive Th2 priming of CD4 T cells⁽⁵⁰⁾. We have gone on to show that during the sensitization phase TSLP responsiveness by CD4 T cells is dispensable (SFZ and RP Larson, manuscript submitted). However, it appears to be CD4 T cells rather than DCs that require TSLP responsiveness during the challenge phase. Two groups, one using epicutaneous antigen challenge via tape stripping and one using direct intradermal injection of TSLP, showed that TSLP acted directly on T cells during the challenge phase to potentiate TH2 cytokine production^(21;54). Furthermore, a recent study by Oh *et al.* implicated TSLP in mediating skin fibrosis downstream of IL-13, in part through the stimulation of fibrocyte collagen production⁽⁵⁵⁾. In the setting of chronic high TSLP expression, skin inflammation also occurred in the absence of T cells⁽⁴⁴⁾, possibly due to the ongoing stimulation of innate immune cells by TSLP. Taken together, these data show that TSLP can act at both the sensitization and challenge phases of an allergic response, and that the target cells at each phase likely differ.

TSLP has also been implicated in the phenomenon referred to as the atopic march, which describes the increased likelihood of individuals with AD of developing allergic rhinitis (AR) and asthma later in life⁽⁵⁶⁾. Several models of induced TSLP expression in mouse keratinocytes result in subsequent allergic airway inflammation following intranasal challenge, suggesting that TSLP may be an important factor contributing to this progression from AD to AR and asthma^(57;58). One caveat of these studies is that they use methods to induce TSLP expression that result in artificially high systemic levels of TSLP not seen in AD patients. We have developed a novel model to test the role of TSLP in the atopic march, using intradermal administration of TSLP with an antigen, followed by intranasal challenge with the antigen alone. Not only does this protocol trigger progression from atopic dermatitis to asthma in the absence of systemic TSLP, but we also found that TSLP was not required for the development of the airway inflammation⁽⁵⁹⁾. These data suggest that the primary role of TSLP is the establishment of allergen-specific Th2 response, and that responses to subsequent challenge with the allergen are driven by other factors. These models, as well as approaches that allow for more specific expression or deletion of TSLP, will be helpful in identifying the cellular targets of TSLP and the mechanisms involved in the progression from AD to AR and asthma.

Asthma—A potential role for TSLP in airway inflammation was first suggested by the finding that TSLP mRNA was present in human lung fibroblasts and bronchial epithelial and smooth muscle cells⁽²⁾, and that aberrant levels of TSLP were associated with certain human respiratory disorders^(4;60–66). For example, lung epithelium and submucosa samples from asthmatics and chronic obstructive pulmonary disease (COPD) patients contained a greater number of TSLP mRNA positive cells, and bronchoalveolar lavage (BAL) samples from these patients had higher concentration of TSLP protein compared to healthy controls^(4;61;63;65). Although the extent of TSLP expression was variable between asthmatic patients, expression was shown to correlate directly with Th2 cytokine and chemokine expression and inversely with lung function^(61;65). Genetic studies also support a critical role for TSLP in allergic airway disease. Several SNPs at the TSLP genomic locus found across multiple ethnic backgrounds were associated with increased asthma susceptibility or protection^(67–71). Importantly, in a large meta-analysis of North American genome-wide association studies in asthma, TSLP was one of 5 genes that reached statistical significance⁽⁷²⁾. One such SNP present in the genomic TSLP locus creates a novel AP-1 transcription factor binding site that could potentially lead to increased TSLP transcription⁽⁶⁷⁾.

A role for TSLP in human asthma has been well supported by a variety of mouse models. These models have shown that TSLP is both necessary and sufficient for the development of type-2 airway inflammation. For example, in the classic ovalbumin prime/challenge model of acute airway inflammation mice lacking TSLP response failed to develop airway inflammation^(22;23). In this model TSLP was shown to be elevated in the lungs of wild-type mice⁽²³⁾, and transfer of activated, OVA-specific wild-type CD4 T cells into TSLPR-deficient hosts rescued aspects of the inflammatory response⁽²²⁾. This is consistent with data mentioned above that TSLP responses in CD4 T cells are important for the challenge phase.

In addition, models using either lung-specific expression of a TSLP transgene, or intranasal administration of TSLP, have demonstrated that elevated TSLP levels in the lung are sufficient to drive an inflammatory response⁽²³⁾. These responses require antigen as well, suggesting that TSLP is actually modifying the response to aero-antigens to promote inflammation⁽⁷³⁾. The phenotypic changes seen in the lung-specific TSLP transgenic strain, in which TSLP is constitutively expressed by the lung epithelium under control of the surfactant protein C (SPC) promoter, closely resembles that seen in humans with asthma. These mice develop a progressive asthma-like disease characterized by lung infiltration of eosinophils and Th2 CD4⁺ T cells, airway remodeling, goblet cell metaplasia and mucus overproduction and airway hyperreactivity. Disease in these mice was largely dependent on IL-4, IL-13, CD4⁺ T cells and antigen^(73;74). CD4⁺ T cells and antigen were also required in an acute airway inflammation model using intranasal administration of TSLP in conjunction with antigen^(73;75).

Most data currently point to a primary role for TSLP in the sensitization/priming stage of allergic airway disease. TSLP produced by activated human-derived lung cells stimulated human DCs to prime CD4⁺ TH2 cell development and mast cell production of TH2-associated cytokines^(2;32;76). Several studies have strongly suggested that DCs are the primary target of TSLP during sensitization and are responsible for the disease phenotype observed in mouse models of airway inflammation^(23;75;77;78). TSLP-induced DC expression of costimulatory molecules, in particular OX40L, and production of the CCR4 ligands CCL17 and CCL21, are important in this response^(23;75;79). However, TSLP also plays a role in the challenge phase of allergic airway disease, largely by supporting Th2 CD4⁺ T cell proliferation and cytokine production^(3;21;22;77;78;80).

TSLP may also influence the regulatory T cell compartment to affect allergic airway disease, as TSLP inhibited IL-10 mediated Treg function and the formation of inducible Tregs to exogenous antigen⁽⁸¹⁾. Importantly, this study showed that BAL fluid from asthmatics inhibited pulmonary Treg function in a TSLP-dependent manner. Additionally, in the OVA/alum model, nucleotide-binding oligomerization domain-containing protein 2 (Nod2), and to a lesser extent Nod1, stimulation blocked tolerance to OVA intranasal challenge in a TSLP- and OX40L-dependent manner⁽⁷⁹⁾. In this model, loss of TSLP signaling correlated with increased antigen-specific FOXP3⁺ T cells following Nod2 stimulation. Using this same model, Lei *et al.* showed that the generation of antigen-specific regulatory T cells was inhibited by TSLP⁽³⁰⁾. TSLP and other allergic diseases. In addition to AD and asthma, elevated TSLP expression has been seen in a variety of other allergic inflammatory conditions. These include allergic rhinitis^(5;82;83), food allergy⁽³⁵⁾, allergic conjunctivitis^(84;85), chronic sinusitis⁽⁸⁶⁾, nasal polyposis^(64;87), and the response to a wide variety of allergens^(39;75;88;89). In addition, TSLP has been associated genetically with eosinophilic esophagitis, a Th2-type inflammatory disease of the esophagus^(90;91).

Clinical perspectives—Collectively, these data argue that the TSLP/TSLPR axis is an attractive therapeutic target for the treatment of allergic inflammatory diseases. Since it is aberrant expression of TSLP that is associated with human allergic disease, blockade of the receptor or neutralization of the cytokine is a logical starting point. In fact, Phase 2 studies are underway using a fully-humanized anti-TSLP antibody (AMG 157 from Amgen Corp.), with asthma as the indication. Other likely indications include atopic dermatitis and respiratory virus-mediated asthma exacerbations. In addition, Genentech has a human monoclonal antibody against OX40L that is currently also in Phase II trials for asthma. As described above, TSLP induces the expression of OX40L on dendritic cells, and OX40-OX40L interactions between DCs and CD4 T cells can drive Th2 differentiation⁽²⁵⁾. Blocking this pathway has been shown to block allergic airway inflammation in mice and in non-human primates⁽⁷⁵⁾. Addressing the outstanding questions of where and when TSLP acts during allergic disease will greatly aid and guide these clinical trials, as will the development of more physiological animal systems for use as pre-clinical models.

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Abbreviations used

TSLP	thymic stromal lymphopoietin
DC	dendritic cell
STAT	signal transducers and activators of transcription
JAK	Janus kinase
AD	atopic dermatitis
SPINK5	serine protease inhibitor Kazal-type 5
COPD	chronic obstructive pulmonary disease
LC	Langerhans cell
AR	allergic rhinitis
FITC	fluorescein isothiocyanate

BAL	bronchoalveolar lavage
Nod2	nucleotide-binding oligomerization domain-containing protein 2

Glossary

CCL17	CCL17 is also known as thymus and activation regulated chemokine (TARC) which is important in the trafficking of CCR4+ T cells to the skin in patients with atopic dermatitis and which can be induced by allergens such as dust mites.
CCL21	CCL21 is important for the homing of naïve and central memory T cells as well as mature dendritic cells through interactions with CCR7.
COMMON γ	The common γ chain is an integral part of the receptors for IL-2, -4, -7, -9, 13, -15, -21 receptors. Mutations in γc leads to X-linked severe combined immunodeficiency.
CRTH2	CRTH2 is the prostaglandin D2 receptor and a recently described chemoattractant receptor on Th2 cells as well as eosinophils and basophils
Dendritic cells	Dendritic cells (DCs) are a type of antigen presenting cell. Multiple subtypes of dendritic cells exist and have varying functions and migratory properties. Migratory DCs develop from precursors in peripheral tissues and migrate to regional lymph nodes and categorized as CD11b+ or CD11b-. Lymphoid tissue resident DCs express CD4, CD8a, or neither and do not migrate from other tissues but develop and live in the lymphoid tissue. Langerhans cells are migratory DCs that can be tolerogenic and by presenting self antigens and producing IL-10. Plasmacytoid DCs are lymphoid DCs that are poor at antigen presentation and make large amounts of IFN α .
IL-7	IL-7 is a proliferation signal for T and B cells and signals through the IL-7 receptor which includes IL-7R α chain and the common gamma chain (γc). More recently IL-7 and IL-7R have been shown to be important for innate helper cell development.
NKT CELL	Natural Killer T (NKT) cells are $\alpha\beta$ T cells that are CD1d restricted and which have been reported to be elevated in severe, poorly controlled asthma
Nod	Nods are pattern recognition receptors that detect muropeptides from bacterial peptidoglycan and which are expressed in epithelial cells, neutrophils, and dendritic cells. An absence of Nod signaling is associated with abnormalities in gastrointestinal microflora control and formation of intestinal lymphoid follicles. Mutations in Nod2 are associated with Crohn's disease.
OVALBUMIN PRIME/CHALLENGE MODEL	Murine asthma models involve a sensitization period (often intraperitoneal on days 0, 12) followed by allergen challenge. Short allergen challenge (often 3 challenges over 1 week) results in an "acute" model of Th2 and eosinophilic airway inflammation; longer allergen challenges cause chronic inflammation and airway remodeling.

OX40L	OX40 is expressed on T cells while OX40 ligand (OX40L) is expressed on dendritic cells. OX40-OX40L interactions promote Th2 polarization and production of eosinophil promoting interleukins such as IL-5 as well as IL-4 and -13. Anti-OX40/40L biologics are in clinical trials for adult allergic asthma
RXR	RXR functions as an obligate heterodimeric partner for multiple nuclear receptors including RAR and the Vitamin D receptor. Once heterodimerized and bound to ligand, RXR complexes bind to a DNA consensus sequences to activate or repress gene transcription
STAT/JAK	The signal transducer and activator of transcription (STAT) family of transcription factors are phosphorylated, dimerized, and bind to palindromic DNA elements in response to Janus activated kinase (JAK) signaling pathways. STATs have a number of roles in allergy. STAT 1, 2 are involved in interferon signaling. STAT3 is downstream of IL-2, -6, -10 signals and IL-23 signaling uses STAT3 for retinoid-related orphan receptor gamma tau (ROR γ t)/Th17 cell phenotype. STAT4 is downstream of IL-12 signaling and activates T-box expressed in T-cell (Tbet) transcription. STAT5 is required for IL-2 stimulated Treg cell development. STAT6 is important for IL-4, -13 dependent gene transcription.
T regs/ FoxP3 T regs	There are various subsets of T regulatory cells including CD4 ⁺ or CD8 ⁺ expressing the transcription factor FoxP3 and/or TGF β , CD25, and IL-10. Naturally occurring T regs come from the thymus while adaptive T regs (also known as Tr1 or Th3 cells) arise in the periphery, are CD80/86 independent, and are antigen-specific. Congenital absence of Foxp3 Treg cells causes Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)

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Figure 1. Schematic representation of the TSLP receptor complex

Schematic of TSLP bound by the TSLP receptor. JAK1 and JAK2, as well as the STAT proteins shown to be activated following receptor engagement, are indicated. STAT5 is in bold as it is the predominant STAT protein that is activated. Listed below are some outcomes of TSLP receptor engagement.

Figure 2. TSLP target cells at mucosal surfaces

Schematic representation of TSLP activity at mucosal surfaces. A variety of stimuli are capable inducing TSLP expression by barrier epithelial cells. TSLP can then activate resident cells, especially dendritic cells, to drive a type 2 response.