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# The importance of TSLP in allergic disease and its role as a potential therapeutic target

**Antonella Cianferoni*** and **Jonathan Spergel**
The Children's Hospital of Philadelphia – Allergy, 3615 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA

## Abstract

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine similar to IL- 7, whose gene is located on chromosome 5q22.1 and it exerts its biological function through the TSLP-Receptor (TSLP-R). TSLP is expressed primarily by epithelial cells at barrier surfaces such as the skin, gut and lung in response to danger signals. Since it was cloned in 1994, there has been accumulating evidence that TSLP is crucial for the maturation of antigen presenting cells and hematopoietic cells. TSLP genetic variants and its dysregulated expression have been linked to atopic diseases such as atopic dermatitis, asthma, allergic rhinitis and eosinophilic esophagitis.

### Keywords

asthma; atopy; eczema; Eosinophilic esophagitis; TSLP; TSLP-R

Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine that exerts its biological function through TSLP receptor (TSLPR), and it plays an important role in many atopic diseases [1–3]. Since it was cloned in 1994, there has been accumulating evidence that TSLP is crucial for the maturation of APCs, and for skewing a T-helper immune response toward the Th2 phenotype, typical of allergic inflammation (Figure 1) [2,3]. TSLP genetic variants and its dysregulated expression have been linked to atopic diseases such as atopic dermatitis (AD), asthma, allergic rhinoconjunctivitis (AR) and eosinophilic esophagitis (EoE), but also to other immune-mediated diseases such as cancer [4–6], rheumatoid arthritis [7] and immune defense against helminth [8]. In the present article, we will review TSLP biology and regulation and its role in atopic diseases.

## Atopy

To better understand the role of TSLP in allergic inflammation, it is important to briefly review the major key immunological features of atopy.



*Author for correspondence: cianferonia@email.chop.edu.

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Atopy is an inflammatory process that occurs due to an abnormal immunological reaction against environmental and food allergens, and it can be IgE mediated, non-IgE mediated (i.e., cell mediated) or mixed IgE and non-IgE mediated [9–14]. Atopic inflammation causes diseases such as asthma, AR, AD, food allergies and EoE [9–14]. It is due to a T-helper type 2 (Th2) inflammation that drives hyperrespon-siveness to stimuli and remodeling of tissues. Th2 inflammation is driven by Th2-type cytokines, such as IL-4, IL-5 and IL-13, secreted by the Th2 subtype of Th2 cells and by many other cells belonging to the innate immunity such as eosinophils, basophils, mast cells, macrophages, invariant natural killer T cells (iNKTs) and innate helper type 2 cells (ILC2) [9–16].

Th2 cells develop from naïve T-helper cells that are primed by an antigen presented by APCs in the presence of IL-4, and this development is driven by the activation of GATA-3, a transcription factor that drives Th2 differentiation by potentiating transcription of the linked, *Il4*, Il13 and Il5 genes [17]. APCs (i.e., Langerhans cells (LCs), macrophages, dendritic cells and B cells) are central to the development of Th2 immunity because antigen presentation is required to initiate responses. Substantial evidence demonstrates that reciprocal cytokine interactions involving APCs regulate the balance between Th1 and Th2 response patterns, for example, APCs secrete the Th2-associated cytokine IL-10 [18], which inhibits APC IL-12 production and thereby drives IL-4 production and GATA3 expression [17,19]. However, the underlying mechanisms leading to the decision as to whether a Th1 or Th2 cytokine pattern predominates in a given response are still not clearly defined.

A novel subset of monocytes called innate helper type 2 cells (ILC2, also known nuocytes, natural helper cells) are novel Th2 cytokine-producing cells that may play a major role in allergic disease. First described in 2001 by Fort *et al*. [20] as non-B/non-T cells that produced IL-5 and IL-13 in response to IL-25 and expressed MHC class $II^{high}$ and $CD11c^{dull}$, these cells have now been better defined by expression of many surface markers such as the prostaglandin D2 (PGD2) receptor CRTH2, CD7, CD25, CD62L, CD127, CD161, CRTH2, ST2 (IL-33R), ALX, CMKLR1, NKG2D, c-kit and DR3 [21–25]. Human ILC2 are present in the gastrointestinal tract, lung, nasal polyp tissue and peripheral blood and have been shown to be activated not only by IL-25 and IL-33 as initially reported but also by a number of cytokines and other inflammatory mediators such as TSLP [22], TNF superfamily member TL1A [25] and IL-9 [26], eicosanoids, arachidonic acid-derived lipid mediators (i.e., PGD2 [24,27], leukotrien D4 [28]). ILC2s are good producers of Th2 cytokines, such as IL-13, IL-5, IL-9, IL-6 and the EGFR ligand amphiregulin [27,29–31]. Not surprisingly, ILC2 highly expresses the master Th2 cytokine transcription factor GATA3 that is required for ILC2 Th2 cytokine production [21,22,32,33]. Even if both conventional Th2 cells and ILC2 express GATA3, ILC2 already express GATA3 in the bone marrow, suggesting they are primed for Th2 cytokine production without the peripheral differentiation that is necessary for Th2 development [21,33]. Overall, these reports suggest that the variable cytokine production by ILC2 may play distinct roles depending on the inflammatory context.

Most of the inflammatory cells are recruited through epithelial-derived chemokines such as Rantes and Eotaxin, which are secreted in response to Th2 cytokines or epithelial damage in genetically predisposed individuals [34,35]. Enzymes and cytotoxic products secreted by

inflammatory cells such as eosinophils, mast cells, $CD8^+$ cytotoxic T cell and iNKTs lead to tissue damage. Th2 cytokines, especially IL-13, favor repair characterized by excessive fibrosis and tissue remodeling, causing permanent and long-lasting damage in tissue affected by Th2 inflammation [9–14].

IgE-mediated classic allergic reactions are due to the presence of allergen-specific IgEs, which bind to its high-affinity receptor (FcεRI) expressed on mast cells and basophils. When specific antigens engage the IgE linked to the FcεRI, they establish receptor cross-linking and the consequent release of mediators [12,36]. Even if initially it was thought that mast cells were the principal effectors cells in IgE-mediated acute reactions, further studies have shown that basophils also play a major role [37,38]. Typical examples of IgE-mediated reactions are acute food allergy reactions, or acute asthma or allergic rhinitis episodes after exposure to environmental allergens. IgE responses can also initiate a delayed chronic inflammation typical of the IgE and non-IgE mixed reactions observed in some forms of chronic asthma, AD and some subtypes of EoE [9–14]. The non-IgE-mediated allergic reactions represent the minority of immunologic responses to environmental and food allergens. They are caused by T-cell and eosinophil activation, and they develop in the absence of demonstrable allergen-specific IgE antibodies in the skin or serum [36,39,40].

Allergens are non-dangerous antigens that usually do not elicit any immune response or otherwise elicit a tolerogenic one through activation of a subtype of T cell called Treg characterized by the presence of transcription factor forkhead box 3 [41–47].

Tolerance to an allergen often depends on an intact and immunologically active epithelial barrier (skin, respiratory or gastrointestinal). This barrier includes epithelial cells joined by tight junctions and a thick mucus layer, which create a physical blockade of the antigen, as well as luminal and brush border enzymes, bile salts and extremes of pH, which contribute to make antigens less immunogenic. In addition, innate (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells and toll-like receptors) and adaptive immunity (intraepithelial and lamina propria lymphocytes, Peyer’s patches, IgA and cytokines) provide an active barrier to foreign antigens that are able to go through an intact epithelial barrier and contribute to elicit a tolerotogenic Treg response. In contrast, damaged tissue lets more intact antigen pass through the barrier and when in contact with the immune system an antigen presented through such inflamed tissue causes antigenic sensitization instead of tolerance [48–51]. This is believed to be the basis of the atopic march observed in children with AD, where food allergens first and environmental allergens second are presented by inflamed skin to the immune system inducing a sequential sensitization to allergens [51,52].

## TSLP & TSLPR

TSLP is a four-helix bundle cytokine that it is closely related to IL-7, a member of the hematopoietin family of cytokines. Its name is derived from the fact that TSLP was initially isolated from a mouse thymic stromal cell line and was found to be a growth factor for B lymphocytes [53,54]. A TSLP human homolog was subsequently isolated [55], which was 43% identical at the amino acid level with conserved glycosylation sites and cysteine

residuals [56]. TSLP binds to its receptor (TSLP-R) to exert its biological activities. TSLP-R is a heterodimeric receptor that consists of the IL-7 receptor alpha-chain (IL-7Rα) and the TSLP receptor alpha chain 1 (TSLPRα, also known as CRL2, TSLPR and CRLF2Y), which is closely related to the common receptor-γ chain (γc) that is found in IL-2, IL-4, IL-9 and IL-15 receptor complexes. The functional TSLPR is mainly expressed in hematopoietic cells (dendritic cells [DC], T cells, B cells, natural killer (NK) cells, iNKT, monocytes, basophils, mast cells and eosinophils), liver, brain, skeletal muscle, kidney, spleen and thymus [50,57–59].

The human *TSLP* gene is located on chromosome 5q22.1 next to the atopic cytokine (IL-4, IL5, IL13, IL3) cluster of chromosome 5q31 [56,60]. The mouse gene is located on chromosome 18 [2]. IL-7Rα (CD127) is located on gen 5q.13 and TSLPRα is encoded on Xp22.3; Yp11.3. Two transcript variants encoding different isoforms have been found for this gene [61].

## TSLP regulation

Despite the initial identification of TSLP in the thymus, TSLP is expressed primarily by epithelial cells at barrier surfaces such as the skin, gut and lung [55,56,62,63]. A variety of danger signals and cytokines are able to activate TSLP production (Figure 2). More specifically, infection agents and their products such as respiratory viruses, bacterial peptidoglycan, lipoteichoic acid, double-stranded RNA (dsRNA), as well as cytokines such as IL-4, IL-13, TNF-α and IL-1 and trauma, air pollutants and allergens have been shown to induce TSLP expression by lung-derived parenchymal cells, skin cells and immune cells [64–72]. Specifically, trigger stimuli for TSLP can exert their function by the activation of toll-like receptor 3 [35,61], protease-activated receptor-2 (PAR-2) [69,73] and the transient receptor potential vanilloid type 1 (TRPV1). Toll-like receptor 3 is activated by viral dsRNA and has been shown to activate TSLP in respiratory and esophageal epithelial cells [35,61]. Proteases (such as trypsin and papain) from airborne allergens like Alternaria induce TSLP production in human airway epithelial cells via PAR-2-a G protein-coupled receptor [69]. Finally, TRPV1 is a temperature- and ligand-sensitive $Ca2^{+}$-permeable ion channel activated by pungent extracts, proton, heat and membrane depolarization [73]. TRPV1 is highly expressed in dorsal root ganglia nociceptor neurons, but it is also found on non-sensory tissues including the human epidermal keratinocyte and airway. It has been shown to be able to activate TSLP release from epithelial respiratory cells [73].

To date, the molecular mechanisms that control the expression and release of TSLP are still not completely understood, but monogenetic diseases and mouse models have helped to understand the transcription regulation of TSLP. It appears that TSLP transcription is dependent to a certain extent on $Ca^{2+}$, nuclear factor active T cells and nuclear factor κB (NF-κB) activation [64,73]. For example, a mouse model has demonstrated that TSLP is secreted after activation of the ORAI1/nuclear factor active T cells calcium signaling pathway [74]. Moreover, TSLP is highly overexpressed in Netherton syndrome, a severe skin disease characterized by AD-like lesions. Netherton syndrome is a result of a defect barrier, caused by mutations in the serine peptidase inhibitor Kazal-type 5 (SPINK5) gene, which encodes the serine protease inhibitor lymphoepithelial Kazal-type-related inhibitor

[75]. In SPINK5 knockout (SPINK5$^{-/-}$) mice, the absence of lymphoepithelial Kazal-type-related inhibitor results in unrestrained activity of the serine protease kalli-krein 5, which directly activates PAR-2 and induces NF-κB-mediated overexpression of TSLP without contribution from the adaptive immune system [69,75]

## TSLP-R signaling

TSLPR has low affinity for TSLP, but in combination with IL-7Rα generates a high-affinity binding site for TSLP and triggers signaling through signal transducer and activator of transcription STAT1, STAT3, STAT5 and JAK1 and JAK2 [76]. In approximately 10–60% of patients with B-cell acute lymphoblastic leukemias (ALL) and in some with T-ALL, investigators have described somatic gain-of-function mutations in TSLP-R associated with the aberrant expression of TSLPRα and mutant IL-7R proteins have formed a functional receptor TSLP. In addition, a subset of TSLPRα-overexpressing B-ALLs have a gain-of-function TSLPRα F232C mutation or activating mutations in JAK2 and JAK1. These data confirm that signaling from the TSLPR activates STAT5 by phosphorylation of JAK1 and JAK2 [4–6].

## TSLP & Th2 inflammation

TSLP is a hematopoietic factor that was originally purified as a B-cell stimulatory factor as it promotes the proliferation and differentiation of committed murine B220$^{+}$/IgM$^{+}$ B cells progenitors; however, the role of TSLP in normal B-cell development or during inflammatory responses remains undefined [77]. On the contrary, in the last several years, it has been clearly demonstrated that the major role of TSLP in both humans and mice is to induce a Th2 cellular adaptive response [55]. Indeed, if TSLP-stimulated CD11c(+)dendritic cells (DCs) are primed in an antigen-specific manner (e.g., in an allogeneic culture) in the absence of IL-12, they express OX40 ligand (OX40L-CD134) and therefore promote the development of Th2 differentiated cells [71,78]. Moreover TSLP-activated DCs further favor Th2 inflammation by polarizing CRTH2$^{+}$ Th2 effector memory cells [79] and by hindering the production and/or maintenance of FOXP3$^{+}$ Tregs *in vivo* in airway allergic inflammation [80,81].

TSLP can also directly promote naïve CD4$^{+}$ and CD8$^{+}$ T cells to develop into Th2 cells because TSLPR activation induces IL-4 gene transcription, which in turn further up-regulates TSLPR on CD4$^{+}$ T cells, resulting in a positive feedback loop [82–84]. Naïve human CD8$^{+}$ T cells express low, if any, TSLPR; however, following activation, TSLPR expression is up-regulated [85]. Moreover, TSLP stimulation up-regulates the survival protein Bcl-2 in an STAT5-dependent manner in both CD4$^{+}$ and CD8$^{+}$ T cells [82,85,86].

TSLP not only is able to induce a Th2 adaptive immune response, but in the last few years it appears to play a major role in favoring the development of Th2 innate immune cells. For example, ILC2, mast cells, NKT cells, basophils and eosinophils express the TSLPR. They respond to TSLP with enhanced Th2 cytokine production, contributing significantly to the Th2 inflammation in AD, asthma and EoE [87–90].

In the last 2 years, there have been several studies focusing on the role of TSLP in ILC2 cells. Indeed these innate cells, which are good producers of Th2 cytokines, appear to be strongly induced by TSLP. In particular, TSLP is able to enhance IL-4, IL-5 and IL-13 expression in IL-33-stimulated human ILC2 purified from peripheral blood and nasal polyps [22]. TSLP has also been shown to activate mouse lung and skin ILC2 [91,92]. Indeed, even if they were initially described to produce high levels of IL-5 and IL-13 and very low levels of IL-4 in response to IL-33, when stimulated with TSLP and leukotriene D4, they are able to produce IL-4, suggesting that ILC2 can also be a good source of IL-4 and therefore could be important in creating the right IL-4-rich environment able to make Th2 development possible when APCs present the antigen to naïve T cells [22,28]. Importantly, a recent study demonstrated that TSLP further enhances GATA3 expression in human ILC2 and thus may be one mechanism of ILC2 Th2 cytokine production induced by TSLP [22].

Finally, TSLP has been shown to promote activity and chemotaxis of eosinophils [90]. Indeed, human eosinophils constitutively expressed functional TSLPR. *In vitro*, in a concentration-dependent manner, TSLP can significantly delay eosinophil apoptosis, up-regulate cell surface expression of adhesion molecule CD18 and intercellular adhesion molecule-1, but down-regulate L-selectin, enhance eosinophil adhesion onto fibronectin and induce the release of inflammatory cytokine IL-6 and chemokines CXCL8, CXCL1 [90]. Hence, TSLP can significantly induce eosinophilic inflammation.

## TSLP & atopic dermatitis

Several lines of evidence support the strong role that TSLP has in AD development.

TSLP has been linked with AD by the association with SNPs in the TSLP gene and its receptor [93–95]. AD had been shown to be significantly associated with four *TSLP*-SNPs (rs1898671, rs11466749, rs10043985 and rs2289276AD) [93,96] and with two *IL7R*-SNPs (rs12516866; rs1053496) (Table 1) [93]. This is not surprising as there are many clinical data that point to a strong genetic component in AD. Indeed, family history of atopy is frequently positive in children with AD [93–95].

From an immunological point of view, increased expression of TSLP is recognized to be a pivotal pathogenetic factor in AD development. TSLP protein is undetectable in non-lesional skin in healthy individuals and in AD patients [63,71]; however, TSLP is highly expressed in acute and chronic AD lesions [71,97]. In particular, it is overexpressed in the skin stratum corneum and it correlates with severity scoring of AD index and epidermal barrier function, such as stratum corneum hydration and transepidermal water loss [97]. Interestingly, moisturizer application results in reduced skin TSLP levels and reduced AD symptoms and scores [97]. In a mouse model, overexpression of skin TSLP was enough to induce a disease phenotype similar to AD [98].

One of the major questions is why TSLP is dysregulated in AD. One possible mechanism is that TSLP is increased due to skin injury (chronic itch in AD or underlying skin defect) and/or Notch signaling impairment, which is common in AD. Indeed, AD epidermis has a marked deficiency of Notch receptors [99], which has been linked to increased TSLP expression. In a mouse model, Notch signaling defects in keratinocyte cause severe

epidermal differentiation defects (dry skin, signs of scratching, skin barrier abnormalities, increased transepidermal water loss) and high systemic levels of TSLP with associated Th2 cell-mediated immunological changes [100]. In addition, Notch signals are critically involved in the differentiation of Treg cells, in the feedback inhibition of activated innate immunity, and in late epidermal differentiation associated with filaggerin- and stratum corneum barrier lipid processing [99]. Specifically, Notch signaling regulates the homeostasis of aqua-porin 3 and of the tight junction component claudin-1 and Notch1 is a repressor of activator protein-1, which is up-regulated in AD epidermis and leads to increased IL-31 [99]. However, TSLP expression may be due to skin barrier defects that are known to directly induce TSLP [101,102] rather than resulting directly from the loss of keratinocyte-specific Notch [100]. Regardless, a reduced Notch signaling may act synergistically with TSLP to increase Th2 inflammation.

Excessive vitamin D levels may also cause an increase in TSLP levels, as TSLP in the skin is negatively regulated by retinoid X receptors (RXRs). In mice, keratinocyte-specific ablation of the RXR (RXRα and RXRβ) resulted in the up-regulation of TSLP and development of AD-like skin inflammation [103]. RXRs are inhibited by vitamin D as it binds vitamin D receptor, and indeed vitamin D or its analogs induce TSLP expression and result in AD development [104,105].

Demethylation of TSLP promoter may also play a role to determine increased TSLP expression in eczema lesions in children with AD. mRNA and protein levels of TSLP measured in lesional skin samples from 10 children with AD and 10 healthy controls showed that levels were increased in skin lesions from patients with AD compared with healthy controls. Such levels were associated with promoter hypomethylation of the TSLP gene in skin lesions from patients with AD. Reversing methylation level by treating keratinocytes with 5-azacytidine, a DNA methyltransferase inhibitor, caused an increase in TSLP. Therefore, in keratinocytes, DNA demethylation of a specific regulatory region of the TSLP gene may contribute to TSLP overexpression in skin lesions in patients with AD [106].

Elevated TSLP activates several positive feedback loops that contribute to AD chronicity and its severity. TSLP and IL-31, another cytokine elevated in AD, stimulate sensory cutaneous neurons involved in the induction of itch. Recently, it has been shown that in skin keratinocytes, TSLP acts directly on a subset of TRPA1-positive sensory neurons to trigger itch [74]. This phenomenon may cause a positive feedback mechanism as skin mechanical injuries such as tape stripping have been shown to up-regulate TSLP levels in the skin [101,102]. Moreover, TSLP in AD potentiates TH2 inflammation by acting directly on Th2-secreting immune cells belonging to both the innate and the adaptive immune system or indirectly by inducing APCs to favor a Th2 response and Th2 cytokines, which are known stimuli for TSLP [38,67,77,82].

TSLP has been shown to act directly on T cells, iNKT, eosinophils, basophils and mast cells to potentiate TH2 cytokine production (Table 1) [65,89,101,107]. In mice, it has also been found that TSLP can also induce the proliferation and differentiation of mast cells from bone marrow progenitors in a STAT6-dependent manner. TSLP-deficient mice have significantly

reduced populations and maturation of mast cells and reduced expression of STAT6. TSLP-induced mast cell proliferation was also abolished by depletion of STAT6. These observations suggest that TSLP is a factor for mast cell development in mice and that it may aggravate mast cell-mediated immune responses [108]

In addition, TSLP has been shown to favor LC migration, maturation and activation as well as DC polarization, which elicit an *in situ* Th2 response in human AD skin lesions [71,102]. TSLP appears also to be important in mediating skin fibrosis through IL-13-induced collagen production [109]. Given such broad direct and indirect effects on the immune system, it does not surprise that in the setting of chronic high TSLP expression, skin inflammation can also occur in the absence of T cells [98].

What is less clear is whether TSLP influences the initiation and/or progression of allergic skin inflammation [110,111]. In addition, clarification is needed to define how crucial TSLP is in the phenomenon referred to as the *atopic march*, which describes the increased likelihood of individuals with AD of developing food allergy, AR and asthma later in life [13,52]. Several mouse models that had artificially high systemic levels of TSLP expression typical of a patient with AD seem to suggest a role of TSLP for the progression from AD to subsequent allergic airway inflammation [112–115]. More recently, intradermal administration of TSLP, which more loosely mimics human AD in TSLP expression, triggers progression from eczema to asthma in the absence of systemic TSLP. In such a model, TSLP was only needed during sensitization as the airway response to antigen challenge was TSLP independent [116]. Similarly, in a model of AD, sensitization to food allergens through an atopic dermatitis-like skin lesion was associated with the development of intestinal food allergy, through an expansion of TSLP-elicited basophils in the skin, a stronger specific antigen-specific Th2 cytokine responses, increased antigen-specific serum IgE levels and accumulation of mast cells in the intestine [51]. The disruption of TSLP responses or depletion of basophils reduced the susceptibility to intestinal food allergy, whereas transfer of TSLP-elicited basophils into intact skin promoted disease, suggesting that both TSLP and basophils were essential to promote food sensitization through the skin [51]. These data suggest that TSLP is important for at least initiation of the atopic march and possibly also for its progression.

## TSLP, asthma & allergic rhinitis

Extensive research in humans and mice support a role of TSLP in asthma and AR development. Several genetic studies (genome-wide and single polymorphism studies) have shown multiple SNPs at the TSLP genomic locus associated with increased asthma susceptibility (rs3806933 [117], rs1837253 [118,119]) or protection (rs1837253 [120], rs2289276 [121]) in different ethnic backgrounds, gender or age. The SNP described by Harada *et al*. [117] in the genomic TSLP locus (rs3806933 (−847C/T) creates a novel activator protein-1 transcription factor-binding site that could potentially lead to increased TSLP transcription (Table 1).

TSLP mRNA is expressed in human lung fibroblasts, bronchial epithelial and smooth muscle cells [71]. TSLP expression both at mRNA and at protein levels appear to be

increased in asthmatic patients and correlates directly with Th2 cytokine and chemokine expression and inversely with lung function [122,123]. Similar results were observed in COPD patients, suggesting that epithelial damage may play a role in driving TSLP expression in the lung in asthma [123]. Increased expression of TSLP in the nasal epithelium has also been found in biopsies from patients with AR and nasal polyps. As for asthma, increased levels of TSLP were associated with Th2-type inflammation [124–126].

Several mouse models support the importance of TSLP in human asthma. If TSLP is overexpressed, because TSLP production either is constitutively activated (i.e., in surfactant protein C (SPC)-TSLP mice, where TSLP in the lung epithelium is under control of the SPC promoter) [127] or is administrated intranasally in conjunction with antigen [128,129], mice develop an asthma-like disease associated with significant Th2 inflammation. $CD4^+$ T cells, Th2 cytokines and antigens played crucial roles in such models, whereas disease symptoms were significantly reduced in the absence of TSLPR or by blocking TSLP activity by antibody or recombinant TSLPR protein [105,127,130–132]. Similar results were obtained in a mouse model of allergic rhinitis [133].

Similar to AD, TSLP seems to induce TH2 inflammation by modulating DC function, promoting Th2 cytokine production from T cells and by inhibiting Treg. The primary target of TSLP in human asthma and mouse models are DCs; hence it appears to influence mostly the sensitization stage of asthma. TSLP-stimulated DCs increase OX40L expression and production of TH2 chemokines, such as CCL17 and CCL21, leading to the priming of $CD4^+$ TH2 cell development and mast cell production of Th2-associated cytokines [65,66,71,105,127,132]. However, TSLP may also influence the challenge stage of allergic airway disease by directly inducing Th2 $CD4^+$ T-cell cytokine production [101,105,130–133]. Finally, TSLP may significantly impair Treg development. Indeed in an allergic airway disease model, TSLP inhibited Treg function and specific antigen Treg development *in vivo* [81,134]. This phenomenon could be mediated trough nucleotide-binding oligomerization domain-containing protein 2 and Nod1 stimulation, which induce TSLP, OX40L and TH2 cytokine expression and inhibit antigen-specific $FOXP3^+$ T cells and ovalbumin (OVA) tolerance [80]. Nod stimulation and other triggers of TSLP expression such as peptidoglycan, lipoteichoic acid, dsRNA, respiratory viruses, air pollutants and allergens most likely act via the NF-κB pathway [64–69,71,72,135]. On the other hand, TSLP transcription in airway epithelial cells is negatively regulated by 9-cis-retinoic acid via RXRs [136]. The regulation of TSLP is a balancing act between negative and positive signals that might affect Treg function.

## TSLP & eosinophilic esophagitis

Many studies have now demonstrated that TSLP is as an important factor for EoE pathogenesis [1,61]. The first indication of TSLP importance in EoE came from the discovery of an association between a SNP in the TSLP gene and risk for EoE. In collaboration with the Center for Applied Genomics at The Children's Hospital of Philadelphia and Cincinnati Children's Hospital, we identified SNP rs3806932 in the promoter region of the TSLP gene. The protective minor allele (G) is present in a higher percentage of control subjects (45.8%) compared to EoE subjects (31.2%) [1]. Individuals

homozygous for the TSLP risk allele (AA) have increased TSLP expression and basophil infiltration in the esophageal epithelium compared to those carrying heterozygous (AG) risk allele and homozygous (GG) protective minor alleles [1]. In addition, Sherrill *et al*. [61] also identified a significant association between a SNP in the TSLP receptor (TSLPR) and male EoE subjects, which is encoded by Xp22.3; Yp11.3 and SNP on X or Y chromosome may affect males specifically (Table 1) [61].

As with other atopic diseases, TSLP is increased in the esophageal biopsies of EoE subjects compared to non-EoE subjects, especially in those that do not carry the protective SNP [1,137,138]. Recent studies from Dr Artis's group [51,137,138] showed that TSLP may promote Th2 inflammation in EoE through basophils. Basophils are known players in type I allergic responses secondary to the surface expression of high-affinity receptor for IgE, FcεRI and their ability to secrete histamine and Th2 cytokines such as IL-4 and IL-13 in an IgE-dependent or -independent manner [16]. Hence recent studies have shown that basophils may play a significant role in non-IgE-mediated allergic conditions such as EoE. Siracusa *et al*. [138] described a sub-population of basophils that developed in the presence of TSLP independently from IL-3. Such a population is overexpressed in allergic disorders, including EoE, and is able to produce significant Th2 cytokines (IL-4, IL-6, CCL3, CCL4 and CCL12). Critically, basophils isolated from EoE subjects exhibited similarities to *in vitro* TSLP-elicited basophils. Noti *et al*. [137] recently described a novel mouse model of EoE in which the development of EoE-like features was dependent upon both TSLP and basophils, but independent of IgE responses. Wild-type and IgE-deficient mice developed similar levels of esophageal inflammation upon antigen challenge, while on the other hand TSLP- or basophil-blocking antibodies ameliorated the EoE-like disease when administered after the onset of disease. Together, these studies show that TSLP-mediated basophil responses might play an important role in the pathogenesis of human EoE and may suggest that targeting the TSLP–basophil axis may lead to potential therapeutic treatments for EoE.
Other potential targets of TSLP in EoE are DC, T cells, iNKTs and Treg. TSLP, as previously discussed, promotes the maturation and activation of DCs, which secrete factors involved in the migration and differentiation of naïve $CD4^+$ T cells into Th2 cells [71]. The currently accepted hypothesis of immune responses in EoE is that antigens penetrate through a dysfunctional esophageal epithelial barrier and are processed by professional APCs such as LCs which in turn promote the polarization of Th2 T cells. TSLP may polarize DCs in genetically predisposed individuals to amplify Th2 responses. However, it is unclear how important the role of esophageal DCs in EoE is, as LCs are present in the esophageal epithelium, but their density is similar in EoE and non-EoE populations [139]. Furthermore, there is clinical knowledge that patients receiving enteral nutrition via post-pyloric feeding tubes can develop EoE, suggesting that direct contact between food antigens and the esophageal epithelium is not a requirement for disease pathogenesis. TSLP could, however, directly influence T cells and iNKTs to produce Th2 cytokines. Indeed, intraepithelial T lymphocytes are the single most prominent infiltrating cell type in EoE. In EoE patients, T cells are Th2-skewed and secrete Th2 cytokines: IL-4, IL-5 and IL-13 in both the peripheral blood and active esophageal biopsies [14,140]. In addition, mice deficient in T cells do not develop EoE, demonstrating the importance of T cells in EoE development [141]. Jyonouchi *et al*. [35] recently demonstrated that iNKTs, which are a subset of T cells specialized in

their ability to recognize self and foreign lipids, may provide a functional link between cow milk allergy with EoE. Children with active EoE compared to children with inactive EoE and healthy controls had higher numbers of iNKTs, which appeared to be recruited in the esophagus via RANTES. iNKT cells from EoE subjects produced higher levels of IL-13 in response to milk sphingolipid stimulation when compared to non-EoE controls. iNKTs have been shown to have TSLPRs and, in AD, to be more Th2-skewed in the presence of TSLP. These observations suggested that IL-13 production derived from iNKT cells migrating to the esophageal epithelium during active inflammation in EoE could be amplified in the presence of TSLP. An increased number of Treg has been reported in the esophageal epithelium of EoE subjects compared to GERD and healthy controls [142,143]. However, the levels of interleukin-10, an anti-inflammatory cytokine secreted by Tregs, were found to be decreased in EoE subjects. TSLP has been shown to inhibit Treg function, so this could explain the apparent paradox mechanisms in EoE, in which increased Tregs in EoE subjects may be an immune compensatory mechanism to curb inflammation.

## Potential therapeutic benefits

Anti-TSLP antibodies have been shown to be beneficial in various murine models of atopy. In an EoE murine model, anti-TSLP has been shown to block the development of esophageal eosinophilia and food impactions [137]. In models of asthma or allergic rhinitis, TSLP antibodies or antibodies that inhibit TSLPR block symptoms of and CD4 Th2 development [105,127,130–132]. For example, in an asthma model of allergic asthma, animals were sensitized with OVA intraperitoneally, then challenged for 7 days with either aerosolized OVA or intranasally; animals who were pretreated with anti-TSLP neutralizing antibodies or anti-TSLPR antibodies administered before each OVA sensitization showed eosinophilic airway inflammation, goblet cell hyperplasia and Th2 cytokine productions [105,131]. In both models, the alleviating effects of TSLP-blocking were achieved by inhibition of maturation and migration of airway DCs, as well as their ability to initiate CD4+T-cell responses [105,131].

AMG 157, a fully human anti-TSLP monoclonal antibody that specifically binds human TSLP, preventing interaction with its receptor, has been tested in stable adult asthmatic patients. In a double-blind, placebo-controlled study, 31 patients received three monthly doses of AMG 157 (700 mg) or placebo intravenously. The allergen challenges on days 42 and 84 showed an attenuated allergen-induced bronchocon-striction in both early and late asthmatic responses. In the group receiving the antibody, there were also reduced markers of systemic and airway inflammation. Although this was only a proof-of-concept study, which did not determine whether anti-TSLP therapeutics will have clinical impact, these findings are consistent with the animal model findings and confirm that TSLP has a key role in allergic asthma [144]. One of the mechanisms that could be acted upon is that TSLP antibody, by decreasing TSLP, may reduce eosinophilic infiltration, as TSLP is a potent chemoattractant for eosinophils [90].

## Conclusion

TSLP appears to be a specific promoter of atopic inflammation, and it often acts with a positive feedback loop amplifying and leading to the chronicity of Th2 inflammatory responses. Many genetic variants that influence its expression have been described in the last few years. Therefore, several aspecific triggers such as infectious agents may cause its release and initiate a chronic Th2 inflammation in predisposed individuals. Given its important specific role in chronic atopic diseases, TSLP is a promising pharmacological target.

## Five-year view

As the first positive clinical trial for anti-TSLP was shown in asthma, [118], Phase II and III clinical trials will examine the role of TSLP in asthma, atopic dermatitis and EoE. From a mechanistic standpoint, comparison of the different roles of IL33, IL31 and TSLP as danger signals in the epithelium will be elicited.

## Expert commentary

TSLP has been cloned from murine and human cell lines, indicating a broad biologic role. It is an epithelial-derived cytokine that is induced via various signals (trauma, infections or injuries), suggesting that it is key molecule for the start of various atopic diseases. In addition, it is induced by a broad range of factors, which further indicates an important role for the cytokine. In fact, TSLP appears to be a key cytokine for the progression of the atopic march (atopic dermatitis to asthma) and development of EoE in multiple murine models. In these murine models, inhibition of TSLP has shown great promise with almost complete inhibition of disease. The first published human trial in asthma shows similar promise. This indicates that TSLP might be a key molecule in the development of allergic disease, and treatment with anti-TSLP compounds will have important clinical effects.

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**Key issues**

- Thymic stromal lymphopoietin (TSLP) is an epithelial derived cytokine, related to IL7 and interacts with TSLP-receptor.
- TSLP has an important role in the maturation and activation of many blood-derived cells.
- It promotes Th2 cell development via IL4 activation.
- It is linked to Asthma, atopic dermatitis and eosinophilic esophagitis based on genetic analysis.
- Murine models identify TSLP as key molecule for the atopic march.
- TSLP has been identified as an essential molecule in the development of eosinophilic esophagitis in murine models (likely in human disease as well).
- It activates mast cells, eosinophils and basophils for allergic inflammation.

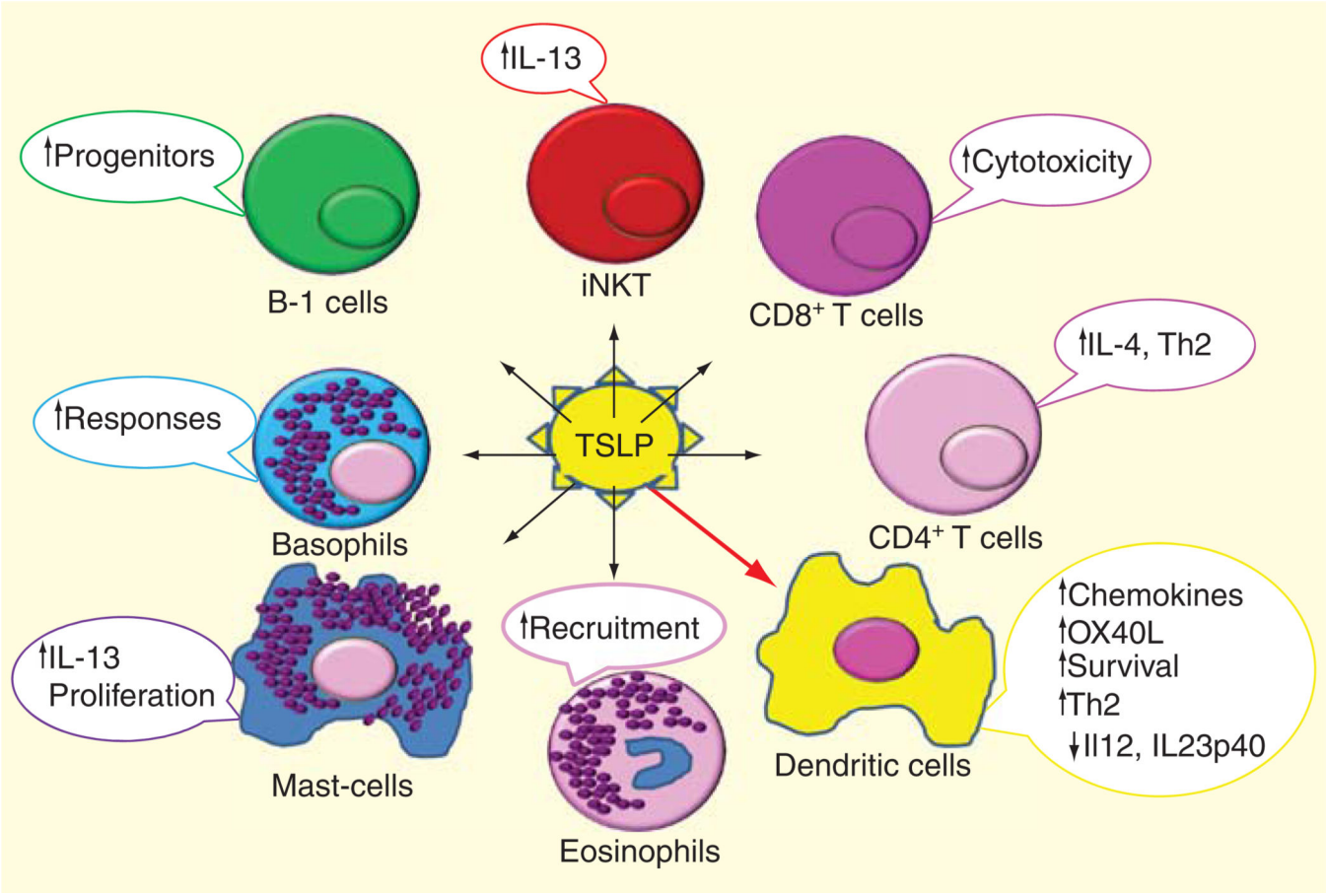


**Figure 1. TSLP effect on different immune cell types to enhance Th2 response**

iNKT: Invariant natural killer T cells; TSLP: Thymic stromal lymphopoietin.

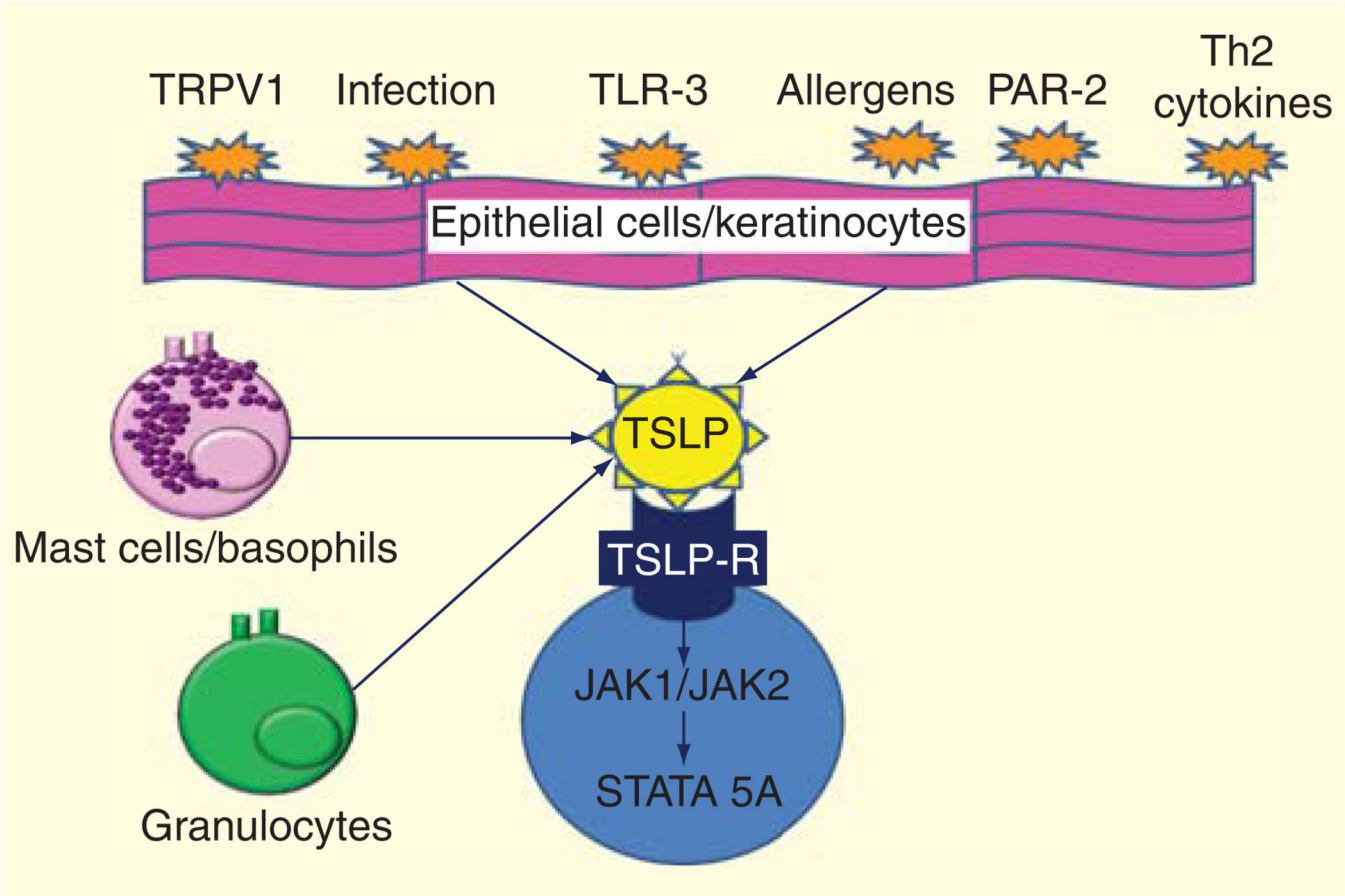


**Figure 2. Cell source of TSLP and stimuli that are able to activate TSLP production**
TSLP: Thymic stromal lymphopoietin.

## Table 1

SNP in TSLP and TSLP receptor associated with major atopic diseases.

| | TSLP SNP | TSLP-R SNP |
|---|---|---|
| Atopic dermatitis | rs11466749 rs10043985 rs2289276 | rs12516866 rs1053496 |
| Asthma | rs3806933, rs1837253, rs1837253, rs2289276 | |
| EoE | rs3806932 | rs36133495 |

EoE: Eosinophilic esophagitis; TSLP: Thymic stromal lymphopoietin; TSLP-R: TSLP-Receptor.