

Mechanisms of allergic diseases

Series editors: Joshua A. Boyce, MD, Fred Finkelman, MD, and William T. Shearer, MD, PhD

Thymic stromal lymphopoietin and allergic disease

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The importance of the epithelium in initiating and controlling immune responses is becoming more appreciated. For example, allergen contact first occurs at mucosal sites 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 human subjects and murine 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 role could potentially allow for novel therapeutic manipulations of these disorders. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Thymic stromal lymphopoietin, asthma, allergy, atopic dermatitis, inflammation

The atopic diseases consist of the triad of asthma, allergic rhinitis (AR), and atopic dermatitis (AD). These diseases share a common pathogenesis involving inflammatory T_H2 -type cytokines and increased IgE levels. Interestingly, they frequently present together in the same subject and family, suggesting common factors and mechanisms are involved in these diseases. Recent evidence has been accumulated to suggest that T_H2 -type $CD4^+$ T cells play a triggering role in the activation, recruitment, or both of IgE antibody-producing B cells, mast cells, and eosinophils (ie, the cellular triad involved in the allergic inflammation). However, the mechanisms underlying the preferential activation by environmental allergens of T_H2 cells in atopic subjects still remain obscure.

One likely candidate for a factor involved in the initiation of allergic inflammatory responses is the cytokine thymic stromal

Abbreviations used

AD:	Atopic dermatitis
AR:	Allergic rhinitis
DC:	Dendritic cell
FITC:	Fluorescein isothiocyanate
IL-7R:	IL-7 receptor
JAK:	Janus kinase
LC:	Langerhans cell
LEKTI:	Lymphoepithelial Kazal-type-related inhibitor
NKT:	Natural killer T
Nod:	Nucleotide-binding oligomerization domain-containing protein
NS:	Netherton syndrome
PAR-2:	Protease-activated receptor 2
RXR:	Retinoid X receptor
SNP:	Single nucleotide polymorphism
SPINK5:	Serine protease inhibitor Kazal-type 5
STAT:	Signal transducer and activator of transcription
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin
TSLPR:	Thymic stromal lymphopoietin receptor

lymphopoietin (TSLP). TSLP is expressed by epithelial cells, with the highest levels seen in lung- and skin-derived epithelial cells.¹ Studies with both human and murine $CD11c^+$ **dendritic cells (DCs)** showed that these cells produced **CCL17** and **CCL22**, chemokines capable of attracting T_H2 -type $CD4^+$ T cells, after exposure to TSLP.^{1,2} In addition, when naive $CD4^+$ T cells are primed on TSLP-treated DCs, they take on an inflammatory T_H2 phenotype, producing IL-4, IL-5, IL-13, and TNF- α on restimulation.² It has recently been shown that TSLP is also a potent growth and survival factor for T_H2 effector cells.³ Notably, a relationship between expression of TSLP and the presence of the atopic diseases asthma, AD, and AR 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 in the form of a humanized mAb against TSLP with asthma as the primary indication, and phase I studies have been successfully completed.

TSLP BIOLOGY

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 costimulate thymocyte proliferation and to promote B-cell

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Support was provided by grants AI068731, AR056113, AR055695, HL098067, HL102708, and AR059058 from the National Institutes of Health and a grant from the Asthma and Allergy Foundation of America.

Disclosure of potential conflict of interest: S. F. Ziegler has received research support from the National Institutes of Health; has received lecture fees from the American Academy of Allergy, Asthma & Immunology; and has received travel support from the Federation of Clinical Immunology Societies.

Received for publication April 2, 2012; revised July 2, 2012; accepted for publication July 3, 2012.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2012.07.010>

Terms in boldface and italics are defined in the glossary on page ■■■.

lymphopoiesis.^{9,10} Subsequently, a human homolog was identified by using *in silico* methods.¹¹ Interestingly, human and murine TSLP share modest sequence homology (approximately 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 (thymic stromal lymphopoietin receptor [TSLPR] subunit), which shares 24% identity with the **common γ chain** (γ_c).^{12,13} The functional receptor (TSLPR) was shown to include both the TSLPR subunit and the IL-7 receptor (IL-7R) α chain in both human subjects and mice (Fig 1).^{11,13} The functional TSLPR is expressed by a variety of hematopoietic cell populations, including T cells, B cells, **natural killer T (NKT) cells**, monocyte/macrophages, basophils, and DCs, as well as some nonhematopoietic cell lineages, such as epithelial cells.^{14,15} Although 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, which is involved in **Janus kinase (JAK)** binding.^{13,16}

Little is known as to the signaling pathways that are activated after engagement of the TSLPR complex. Initial studies in the mouse showed that **signal transducer and activator 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, 2 recent articles have demonstrated robust and sustained activation of JAK1 and JAK2 after TSLP signaling in primary human DCs and primary human and murine CD4⁺ T cells.^{17,18} Surprisingly, unlike IL-7R α and γ_c in IL-7 signaling, which use JAK1 and JAK3, the TSLPR subunit bound and used JAK2 in concert with IL-7R α -associated JAK1. 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 human subjects recent studies have shown that, in addition to STAT5, TSLP stimulation activated STAT1, STAT3, STAT4, STAT5, and STAT6, as well as JAK1 and JAK2.¹⁷ One possible explanation for the discrepancy in the data between species is that the murine signaling work used a pre-B-cell line, whereas the human studies were in primary DCs. Consistent with this explanation, our laboratory has shown that TSLP-treated murine DCs activate JAK1 and JAK2, as well as STAT1, STAT3, and STAT5 (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 uses similar signaling

GLOSSARY

CCL17: CCL17 is also known as thymus and activation-regulated chemokine, which is important in the trafficking of CCR4⁺ T cells to the skin in patients with atopic dermatitis and can be induced by allergens, such as dust mites.

CCL21: CCL21 is important for the homing of naive and central memory T cells, as well as mature dendritic cells, through interactions with CCR7.

COMMON γ CHAIN: The common γ chain (γ_c) is an integral part of the receptors for IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, and IL-21. Mutations in γ_c lead to X-linked severe combined immunodeficiency.

CRTH2: CRTH2 (chemoattractant receptor-homologous molecule expressed on T_H2 cells) is the prostaglandin D₂ receptor and a recently described chemoattractant receptor on T_H2 cells, as well as eosinophils and basophils.

DENDRITIC CELLS (DCs): DCs are a type of antigen-presenting cell. Multiple subtypes of DCs exist and have varying functions and migratory properties. Migratory DCs develop from precursors in peripheral tissues, migrate to regional lymph nodes, and are categorized as CD11b⁺ or CD11b⁻. Lymphoid tissue-resident DCs express CD4, CD8 α , or neither and do not migrate from other tissues but develop and live in the lymphoid tissue. Langerhans cells are epidermal DCs that can be both tolerogenic and inflammatory. 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 the IL-7 receptor α chain and the common γ chain. More recently, IL-7 and IL-7 receptor have been shown to be important for innate helper cell development.

NATURAL KILLER T (NKT) CELL: NKT cells are $\alpha\beta$ T cells that are CD1d restricted, with numbers reported to be increased in patients with severe and poorly controlled asthma.

NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN-CONTAINING PROTEIN (NOD): Nods are pattern-recognition receptors that detect muropeptides from bacterial peptidoglycan and 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 disease.

OVALBUMIN PRIME/CHALLENGE MODEL: Murine asthma models involve a sensitization period (often intraperitoneal on days 0 and 12), followed by allergen challenge. Short allergen challenges (often 3 challenges over 1 week) result in an "acute" model of T_H2 and eosinophilic airway inflammation; longer allergen challenges cause chronic inflammation and airway remodeling.

OX40 LIGAND (OX40L): OX40 is expressed on T cells, whereas OX40L is expressed on dendritic cells. OX40-OX40L interactions promote T_H2 polarization and production of eosinophil-promoting interleukins, such as IL-5, as well as IL-4 and IL-13. Anti-OX40/OX40L biologics are in clinical trials for adult allergic asthma.

REGULATORY T (TREG) CELLS/FOXP3 TREGS: There are various subsets of Treg cells, including CD4⁺ or CD8⁺ cells expressing the transcription factor forkhead box protein 3 (FoxP3) and/or TGF- β , CD25, and IL-10. Naturally occurring Treg cells come from the thymus, whereas adaptive Treg cells (also known as T_R1 or T_H3 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) syndrome.

RETINOID X RECEPTOR (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 DNA consensus sequences to activate or repress gene transcription.

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION (STAT)/JANUS KINASE (JAK): The STAT family of transcription factors are phosphorylated and dimerized and bind to palindromic DNA elements in response to JAK signaling pathways. STATs have a number of roles in allergy. STAT1 and STAT2 are involved in interferon signaling. STAT3 is downstream of IL-2, IL-6, and IL-10 signals, and IL-23 signaling uses STAT3 for the retinoid acid-related orphan receptor γ t (ROR γ t)/T_H17 cell phenotype. STAT4 is downstream of IL-12 signaling and activates T-box expressed in T-cell (T-bet) transcription. STAT5 is required for IL-2-stimulated Treg cell development. STAT6 is important for IL-4- and IL-13-dependent gene transcription.

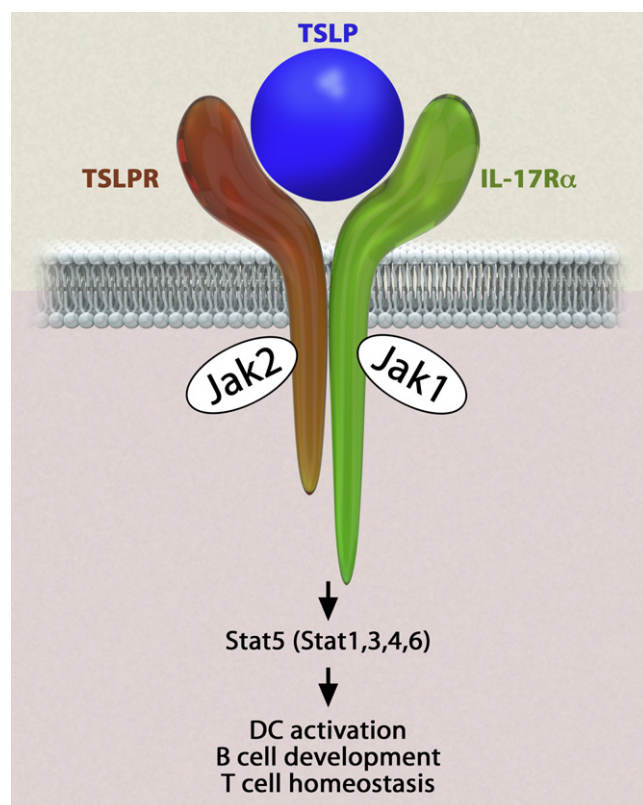


FIG 1. Schematic representation of the TSLPR complex: schematic of TSLP bound by TSLPR. JAK1 and JAK2, as well as the STAT proteins shown to be activated after receptor engagement, are indicated. STAT5 is in boldface because it is the predominant STAT protein that is activated. Listed below are some outcomes of TSLPR engagement.

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 human subjects and mice is composed of myeloid-derived dendritic cells.^{1,23} Coculture of TSLP-activated DCs with naive 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 (eg, in an allogeneic culture), the resulting T cells displayed characteristic features of T_H2 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 T_H2 cell differentiation. Interestingly, TSLP, in the absence of IL-12, induced *OX40 ligand* (*OX40L*) expression on DCs, and OX40-OX40L interactions were critical for the ability of DCs to drive T_H2 cell differentiation.²⁵ Consistent with a role in regulating T_H2 cytokine responses, TSLP-activated DCs were also capable of supporting the maintenance and further polarization of *CRT2*⁺ T_H2 effector memory cells.²⁶

TSLP-conditioned DCs also augmented intestinal epithelial cell-mediated IgA₂ class switching through the induction of a proliferation-inducing ligand.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* (*Treg*) cells,²⁷⁻²⁹ although other studies have indicated that TSLP might hinder the production, maintenance, or both of forkhead box protein 3-positive Treg cells *in vivo* in certain disease processes.³⁰

Finally, several innate immune cells express 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 the direct effects of TSLP on basophils during T_H2 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 (Fig 2). Although the normal function of TSLP is likely the maintenance of T_H2-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 et al² showing increased expression of TSLP in the lesional skin of patients with AD. Since then, numerous studies in both human subjects and mice have implicated TSLP in other atopic diseases, including asthma, AR, 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 might act.

AD

AD is a chronic inflammatory skin disease that affects an estimated 10% to 20% of infants and young children in the United States.³⁶ Although 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 al³⁹ found that TSLP was rapidly induced after 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 subjects experience a significant predisposition for atopic disease,⁴⁰ have increased TSLP levels 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

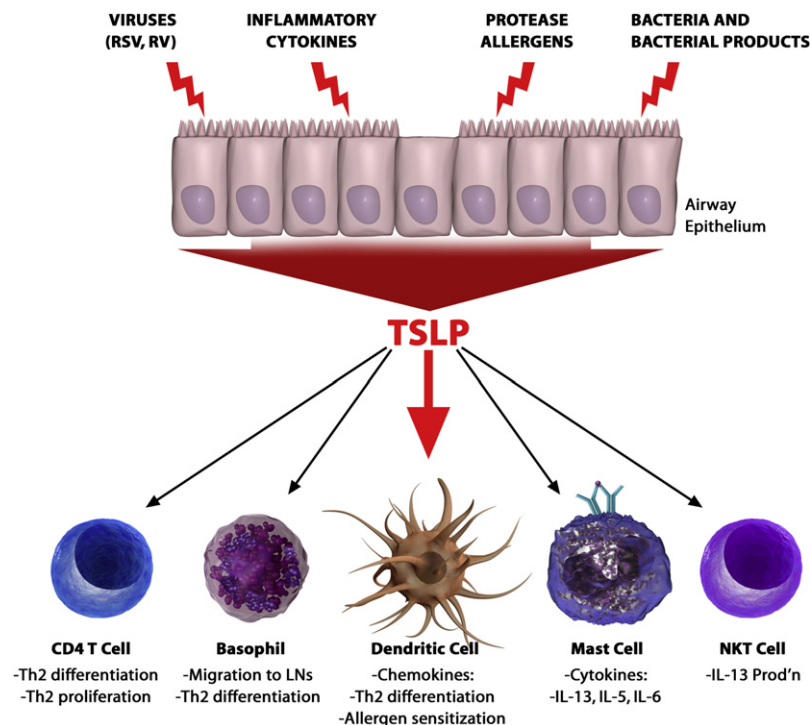


FIG 2. TSLP target cells at mucosal surfaces: schematic representation of TSLP activity at mucosal surfaces. A variety of stimuli are capable of inducing TSLP expression by barrier epithelial cells. TSLP can then activate resident cells, especially DCs, to drive a type 2 response.

(*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 PAR-2 and induced nuclear factor 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 human subjects and mice.

In mice overexpression 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, the presence of T_H2 cells in skin-draining lymph nodes, and the production of type 2 cytokines in the skin. Similarly, using an antigen-driven model of dermatitis that also uses barrier disruption through tape stripping, He et al²¹ found that TSLP signaling was required for the 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 (RXR)* 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 downregulated TSLP expression through inhibition of nuclear factor 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 might result in RXR derepression and recruitment of coactivators 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 might be due to responses to the resulting skin barrier defect rather than directly from the loss of keratinocyte-specific Notch signaling itself because 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 T_H2-mediated model of human allergic contact dermatitis, has recently been elucidated. TSLP expression is induced after 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 do not mount a response after challenge, as did mice in which 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 DCs in TSLPR-deficient mice. Antigen-bearing DCs 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 after FITC sensitization (S. F. Ziegler and R. P. Larson, manuscript in preparation). These data are consistent with TSLP driving CD4 T-cell proliferation indirectly, possibly through activated DCs.

Two important unanswered questions concerning the role of TSLP in allergic inflammation are determining during which phase of the response it exerts 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 might differ depending on the context. Langerhans cell (LC) migration and activation were 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 explant cultures and to condition LCs to prime cocultured naive CD4⁺ T cells to adopt an inflammatory T_H2 phenotype.⁵³ The data in murine models of AD implicate TSLP in both sensitization and challenge but indicate that different cell types appear to be important as targets at each phase. Using a model of hapten-mediated contact hypersensitivity, Larson et al⁵⁰ showed that TSLP is important during sensitization, acting on skin-resident DCs to drive T_H2 priming of CD4 T cells. We have gone on to show that during the sensitization phase, TSLP responsiveness by CD4 T cells is dispensable (S. F. Ziegler and R. P. 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 by means of tape stripping and one using direct intradermal injection of TSLP, showed that TSLP acted directly on T cells during the challenge phase to potentiate T_H2 cytokine production.^{21,54} Furthermore, a recent study by Oh et al⁵⁵ implicated TSLP in mediating skin fibrosis downstream of IL-13, in part through the stimulation of fibrocyte collagen production. In the setting of chronic high TSLP expression, skin inflammation also occurred in the absence of T cells,⁴⁴ possibly because of 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 subjects with AD to have AR and asthma later in life.⁵⁶ Several models of induced TSLP expression in murine keratinocytes result in subsequent allergic airway inflammation after intranasal challenge, suggesting that TSLP might 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 patients with AD. 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 AD to asthma in the absence of systemic TSLP, but we also found that TSLP was not required for the development of airway inflammation.⁵⁹ These data suggest that the primary role of TSLP is the establishment of the allergen-specific T_H2 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 cells²

and that aberrant levels of TSLP were associated with certain human respiratory disorders.^{4,60-66} For example, lung epithelial and submucosal samples from asthmatic patients and patients with chronic obstructive pulmonary disease contained a greater number of TSLP mRNA-positive cells, and bronchoalveolar lavage samples from these patients had higher concentrations of TSLP protein compared with those seen in healthy control subjects.^{4,61,63,65} Although the extent of TSLP expression was variable between asthmatic patients, expression was shown to correlate directly with T_H2 cytokine and chemokine expression and inversely with lung function.^{61,65} Genetic studies also support a critical role for TSLP in patients with 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 asthmatic patients, TSLP was one of 5 genes that reached statistical significance.⁷² One such SNP present in the genomic TSLP locus creates a novel activator protein 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 murine 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 a TSLP response did not have airway inflammation.^{22,23} In this model TSLP levels were shown to be increased 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 the TSLP transgene or intranasal administration of TSLP have demonstrated that increased 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 aeroantigens 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 promoter, closely resembles that seen in human subjects with asthma. These mice have a progressive asthma-like disease characterized by lung infiltration of eosinophils and T_H2 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⁺ T_H2 cell development and mast cell production of T_H2-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 murine 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 T_H2 CD4⁺ T-cell proliferation and cytokine production.^{3,21,22,77,78,80}

TSLP can also influence the Treg cell compartment to affect allergic airway disease because TSLP inhibited IL-10-mediated Treg cell function and the formation of inducible Treg cells to exogenous antigen.⁸¹ Importantly, this study showed that bronchoalveolar lavage fluid from asthmatic patients inhibited pulmonary Treg cell function in a TSLP-dependent manner. Additionally, in the ovalbumin/alum model, nucleotide-binding oligomerization domain-containing protein 2 (*Nod*) 2 and, to a lesser extent, Nod1 stimulation blocked tolerance to ovalbumin intranasal challenge in a TSLP- and OX40L-dependent manner.⁷⁹ In this model loss of TSLP signaling correlated with increased antigen-specific forkhead box protein 3-positive T-cell numbers after Nod2 stimulation. Using this same model, Lei et al³⁰ showed that the generation of antigen-specific Treg cells was inhibited by TSLP.

TSLP and other allergic diseases

In addition to AD and asthma, increased TSLP expression has been seen in a variety of other allergic inflammatory conditions. These include AR,^{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 T_H2-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. Because 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 II studies are underway using a fully humanized anti-TSLP antibody (AMG 157; Amgen, Thousand Oaks, Calif) with asthma as the indication. Other likely indications include AD and respiratory virus-mediated asthma exacerbations. In addition, Genentech (South San Francisco, Calif) has a human mAb against OX40L that is currently also in phase II trials for asthma. As described above, TSLP induces the expression of OX40L on DCs, and OX40-OX40L interactions between DCs and CD4 T cells can drive T_H2 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 physiologic animal systems for use as preclinical models.

I thank Matt Warren for assisting in the preparation of this article.

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