

The multiple facets of thymic stromal lymphopoietin (TSLP) during allergic inflammation and beyond

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ABSTRACT

Originally shown to promote the growth and activation of B cells, TSLP is now known to have wide-ranging impacts on hematopoietic and nonhematopoietic cell lineages, including DCs, basophils, eosinophils, mast cells, CD4⁺, CD8⁺, and NK T cells, B cells, and epithelial cells. Whereas the role of TSLP in the promotion of TH2 responses has been studied extensively in the context of lung- and skin-specific allergic disorders, it is becoming increasingly clear that TSLP may impact multiple disease states within multiple organ systems, including the blockade of TH1/TH17 responses and the promotion of cancer and autoimmunity. This review will highlight recent advances in the understanding of TSLP signal transduction, as well as the role of TSLP in allergy, autoimmunity, and cancer. Importantly, these insights into the multifaceted roles of TSLP could potentially allow for novel, therapeutic manipulations of these disorders. *J. Leukoc. Biol.* 91: 000–000; 2012.

Introduction

TSLP is a member of the IL-2 cytokine family and a distant paralog of IL-7 [1]. Murine TSLP was discovered in thymic stromal cell line supernatants that supported B cell develop-

ment [2]. Like IL-7, TSLP can stimulate thymocytes and promote B cell lymphopoiesis. Accordingly, TSLP was studied initially as a B cell growth factor [3]. A human homolog was identified subsequently, and further characterization of the cytokine revealed a four-helix bundle structure containing six conserved cysteine residues and multiple potential sites for N-linked carbohydrate addition. As discussed later, in spite of only 43% aa identity, human and murine TSLP share a significant degree of functional homology [4–6]. During allergic inflammation, the primary producers of TSLP are epithelial cells, keratinocytes, and stromal cells, although recent data have demonstrated that DCs and mast cells are capable of TSLP production [7–12].

Several groups identified a receptor capable of binding TSLP with low affinity (TSLPR subunit), which shares 24% identity to γ_c [13]. Upon further analyses, the functional receptor (TSLPR) was shown to include the TSLPR subunit and the IL-7R α chain in humans and mice [14, 15]. The functional TSLPR is expressed by a variety of hematopoietic cell populations, such as T cells, B cells, NK cells, monocytes, basophils, eosinophils, and DCs, as well as some nonhematopoietic cell lineages, such as epithelial cells [16, 17]. Although classified as a hematopoietin receptor based on structural homology, the TSLPR subunit contains notable differences from canonical hematopoietin receptors. The TSLPR subunit contains the conserved box1 sequence, which regulates JAK binding in other cytokine receptors but lacks the conserved box2 and contains only one tyrosine residue, 4 aa from its carboxy terminus [15]. Additionally, it contains a modified WSXWS motif and multiple potential N-linked glycosylation sites [18].

TSLP SIGNALING

As a member of the hematopoietin receptor family, it was hypothesized originally that the TSLPR would use JAKs to activate STAT proteins downstream of the TSLPR. Indeed, TSLP

Abbreviations: $^{-/-}$ =knockout, γ_c =common γ receptor chain, AD=atopic dermatitis, ALL=acute lymphoblastic leukemia, AR=allergic rhinitis, B-ALL=B cell acute lymphoblastic leukemia, BMDC=bone marrow-derived DC, CHS=contact hypersensitivity, COPD=chronic obstructive pulmonary disease, CRLF2=cytokine receptor-like factor 2, CRTH2=Chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes, DSS=dextran sulfate sodium, EC=epicutaneous, EoE=eosinophilic esophagitis, FOXP3=forkhead box P3, IBD=inflammatory bowel disease, IEC=intestinal epithelial cell, LEKTI=lymphoepithelial Kazal-type-related inhibitor, mDC=myeloid DC, MS=multiple sclerosis, NE=neutrophil elastase, Nod=nucleotide-binding oligomerization domain, NS=Netherton's syndrome, OX40L=OX40 ligand (CD134), PAR-2=protease-activated receptor 2, RA=rheumatoid arthritis, RXR=single nucleotide polymorphism, SPC=surfactant protein C, SPINK5=serine peptidase inhibitor Kazal-type 5, Treg=regulatory T cell, TSLP=thymic stromal lymphopoietin, UC=ulcerative colitis

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stimulation of multiple cell lines leads to STAT-5 phosphorylation. However, initial experiments in these cell lines showed that TSLPR signaling occurred in the absence of JAK activation, and dominant-negative forms of JAK-1 and -2 did not affect TSLP-mediated STAT-5 activation [3, 19]. Several alternatives were implicated in TSLPR signaling, such as Src kinases and PI3K [20]. However, two recent papers have demonstrated robust and sustained activation of JAK-1 and -2 following TSLP signaling in primary human DCs and primary human and mouse CD4⁺ T cells [21, 22]. Surprisingly, unlike IL-7R α and γ_c in IL-7 signaling, which use JAK-1 and -3, the TSLPR subunit bound and used 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.

Whereas multiple cell lineages express the functional TSLPR and respond to TSLP in vivo, most studies about TSLP-activated signaling pathways have been done in DCs and T cells [16]. TSLP induced STAT-5 and STAT-1 phosphorylation in CD4⁺ T cells [3, 13, 19, 20, 22–24], while activating STAT-1, -3, -4, -5, and -6 in human mDCs [21]. In contrast, our lab found activation of only STAT-1, -3, and -5 following TSLP treatment of murine BMDCs (unpublished results). These data suggest that TSLP is capable of activating multiple STAT proteins (Fig. 1). Whether TSLP uses similar signaling pathways in other cell lineages and how each STAT molecule contributes have yet to be elucidated.

CELLULAR EVENTS DOWNSTREAM OF TSLP SIGNALING

DCs

A hallmark of the action of TSLP on DCs is the up-regulation of cell surface molecules and chemokines, such as CCL17,

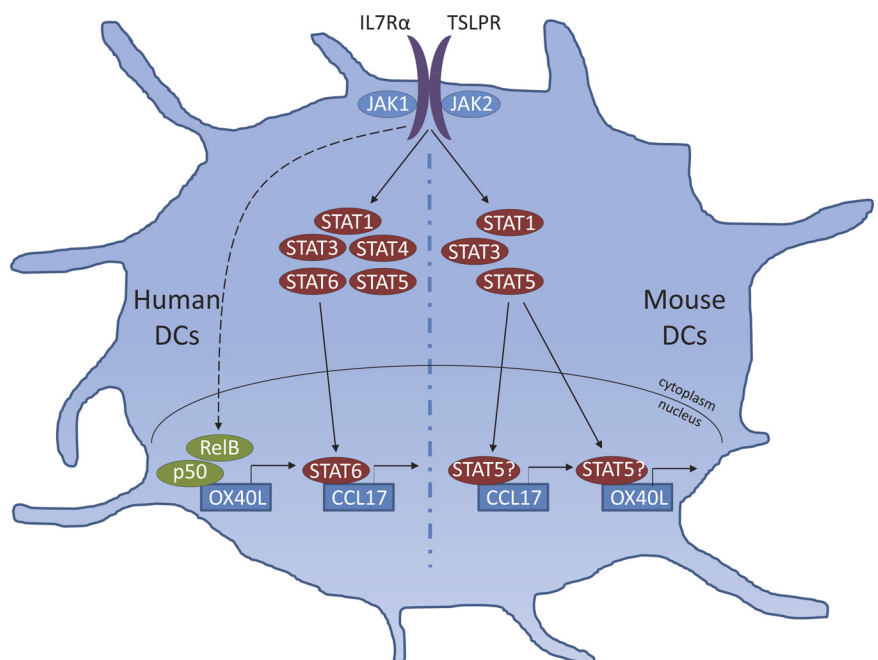
which are involved in TH2 generation and attraction. In in vitro cultures, TSLP stimulated DC up-regulation of CD40, CD80, and CD86. However, in contrast to other stimuli, such as dsRNA, which also up-regulate costimulatory molecules, TSLP preferentially induced OX40L expression through activation of noncanonical NF- κ B signaling, which helps drive TH2 generation [21, 25, 26]. Whereas induction of CCL17 occurred through activation of STAT-6 in human DCs [21], STAT-5, and not STAT-6, was required for TSLP-induced CCL17 production in murine BMDCs (unpublished results).

In humans, allogeneic, TSLP-activated DCs primed naïve CD4⁺ T cells to produce characteristic TH2 cytokines [7, 9]. In contrast, autologous, TSLP-activated DCs supported proliferation but not differentiation of naïve CD4⁺ T cells [9], and supported the expansion and functions of CRTH2⁺ CD4⁺ TH2 memory cells [27]. TSLP-conditioned DCs also augmented IEC-mediated IgA2 class-switching through the induction of a proliferation-inducing ligand (APRIL) [28]. Finally, some in vitro studies have suggested a role for TSLP in the generation of tolerigenic DCs that can drive the differentiation of Tregs [29–31], although other studies have indicated that TSLP may hinder the production and/or maintenance of FOXP3⁺ Tregs in vivo in certain disease processes [32, 33].

T lymphocytes

TSLP can also act directly on T cells and in the presence of TCR stimulation, promoted proliferation and TH2 differentiation of naïve CD4⁺ T cells through induction of IL-4 gene transcription [34, 35]. IL-4 further up-regulated TSLPR on CD4⁺ T cells, resulting in a positive feedback loop. Although IL-4 maintained TSLPR expression on in vitro-differentiated TH2 and TH17 cells, higher TSLPR levels were present on TH2 than on TH1 and TH17 cells, which correlated with the ability of TSLP to drive the proliferation and survival of acti-

Figure 1. TSLP-induced signaling pathways in human and mouse DCs. TSLP activates non-canonical NF- κ B and multiple STAT proteins in human DCs to induce OX40L upregulation and CCL17 production, respectively. Activation of mouse DCs by TSLP induces only STAT-1, -3 and -5, with the latter being responsible for CCL17 production.



vated TH2 cells [36]. Naïve mouse CD8⁺ T cells also express TSLPR, although TSLPR expression is low to absent on naïve human CD8⁺ T cells; however, following activation, TSLPR expression is up-regulated on mouse and human CD8⁺ T cells [24, 37]. In CD4⁺ and CD8⁺ T cells, TSLP stimulation up-regulated the survival protein Bcl-2 in a STAT-5-dependent manner [22, 24, 36].

B lymphocytes

The initial studies describing TSLP demonstrated that TSLP can support B cell lymphopoiesis [2, 3]. In *in vitro* studies, pro-B cells derived from fetal liver, but not BM, responded to TSLP, although pre-B cells from both origins could proliferate in response to TSLP [38]. The role of TSLP in normal B cell development or during inflammatory responses remains undefined; however, as will be discussed later, it is clear that aberrant TSLP signaling can have a significant impact on B cells, as has been demonstrated in mouse models and by the association of mutations around the TSLPR gene locus with a subtype of B cell leukemia [39, 40].

Innate immune cells

Multiple innate immune cells express the TSLPR and respond to TSLP. For example, TSLP can enhance cytokine production from mast cells, NKT cells, and eosinophils [41–43]. Recent work has highlighted direct effects of TSLP on basophils during TH2 cytokine-associated inflammatory diseases, including promotion of basophil hematopoiesis from the BM in an IL-3-independent manner [44].

TSLP-ASSOCIATED DISEASES

The effects of TSLP on various cell types demonstrate that TSLP can impact type 2 inflammation through myriad different pathways. In addition, numerous studies in humans and mice now implicate TSLP in a growing number of different disorders beyond allergic inflammation, including infection, cancer, and autoimmunity. The following sections describe the disorders associated with TSLP and what is known about the mechanisms through which TSLP may act.

Skin disorders

AD is a chronic inflammatory skin disease that affects an estimated 10–20% of infants and young children in the United States [45]. No SNPs in or around the TSLP gene locus have yet been associated with AD [46]. However, whereas TSLP protein was undetectable in nonlesional skin in AD patients, TSLP was highly expressed in acute and chronic AD lesions [7]. TSLP was also overexpressed in the skin of individuals with NS, a severe skin disease characterized by AD-like lesions, as well as other allergic manifestations that result from mutations in the SPINK5 gene, which encodes the serine protease inhibitor LEKTI [47].

In mice, overexpression of TSLP in the skin was sufficient to induce a disease phenotype characterized by all of the hallmark features of AD [48]. In the steady-state, TSLP expression in the skin appears to be negatively regulated by RXRs, as keratinocyte-specific ablation of the RXR isotypes RXR α and

RXR β resulted in up-regulation of TSLP and development of AD-like skin inflammation [49]. RXRs heterodimerize with many nuclear receptor partners, including the vitamin D receptor and peroxisome proliferator-activated receptors. Administration of vitamin D or its analogs up-regulated TSLP and resulted in the development of dermatitis [50], suggesting that vitamin D administration may 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. However, TSLP expression in this model may be a result of responses to the resulting skin barrier defect rather than directly from the loss of keratinocyte-specific Notch signaling itself, as WT and mutant keratinocytes produced similar amounts of TSLP in *in vitro* cultures [51]. In 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 NF- κ B-mediated overexpression of TSLP without contribution of the adaptive immune system [47, 52]. Interestingly, in SPINK5^{-/-}/PAR-2^{-/-} mice, TSLP expression was greatly diminished, although inflammation still occurred [53]. Whether the cytokine milieu differs in the absence of TSLP remains to be determined.

TSLP may influence 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. LC migration and activation were seen in human AD lesions *in situ* [7]. 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, naïve CD4⁺ T cells to adopt an inflammatory TH2 phenotype [54]. However, mouse models of AD implicate additional cell types in the initiation and promotion of AD by TSLP. A recent study by Oh et al. [55] implicated TSLP in mediating skin fibrosis downstream of IL-13, in part, through the stimulation of fibrocyte collagen production. In a model of allergic skin inflammation using EC sensitization to OVA on tape-stripped skin, TSLP acted directly on T cells during the challenge phase to potentiate TH2 cytokine production [56]. T cells were also required for TSLP-mediated dermal inflammation induced through intradermal delivery of rTSLP protein [57]. In contrast, TSLP was involved in sensitization and challenge phases of FITC-mediated CHS, as ear swelling was minimal if blockade of TSLP occurred prior to sensitization but was only modestly reduced when TSLP blockade occurred after sensitization but prior to challenge [58, 59]. Whereas DC migration was intact in the absence of TSLP in EC sensitization, loss of TSLP signaling in the FITC CHS model was associated with reduced migration and activation of skin-derived, antigen-bearing DCs. In addition, TSLP-responsive CD4⁺ T cells were not required to induce a TH2 response in the CHS model (unpublished results). In the setting of chronic high TSLP expression, skin inflammation also occurred in the absence of T cells [48], possibly as a result of the ongoing stimulation of innate immune cells by TSLP.

TSLP has also been implicated in the phenomenon referred to as the atopic march, which describes the increased likeli-

hood of individuals with AD to develop AR and asthma later in life [60]. 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 [61, 62]. Whereas many of these methods used to induce TSLP expression result in artificially high systemic levels of TSLP that are not seen in AD patients, we have found that intradermal administration of TSLP triggers progression from AD to asthma in the absence of systemic TSLP (unpublished results). 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.

Respiratory diseases

The initial report from Soumelis et al. [7], demonstrating high TSLP expression in AD and potentiation of inflammatory TH2 responses by TSLP, also suggested a potential role for TSLP in allergic airway disease. This hypothesis was supported by the demonstration that TSLP mRNA was present in human lung fibroblasts and bronchial epithelial and smooth muscle cells and that aberrant levels of TSLP were associated with certain human respiratory disorders [10, 63–69]. Lung epithelium and submucosa samples from asthmatics and COPD patients contained a greater number of TSLP mRNA-positive cells and BAL samples from these patients had a higher concentration of TSLP protein compared with healthy controls [10, 64, 66, 68]. Although the extent of TSLP expression can be variable in asthmatic patients, it has been shown to correlate directly with TH2 cytokine and chemokine expression and inversely with lung function [64, 68]. Increased expression of TSLP in the nasal epithelium has also been found in biopsies from AR patients and was associated with TH2 cytokines and eosinophils in epithelial-associated tissue [65, 67, 69, 70]. 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 [71–78]. 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 [71].

A role for TSLP in human asthma has been well supported by a variety of mouse models, such as the SPC-TSLP mouse, in which TSLP is constitutively expressed by the lung epithelium under control of the SPC promoter [26]. With increasing age, these mice developed a progressive asthma-like disease characterized by lung infiltration of eosinophils and TH2 CD4⁺ T cells, airway remodeling, and airway hyperreactivity. Disease in these mice was largely dependent on IL-4, IL-13, CD4⁺ T cells, and antigen [79, 80]. CD4⁺ T cells and antigen were also required in an acute asthma model, using intranasal administration of TSLP in conjunction with antigen [79, 81]. In addition to driving allergic inflammation in the lung following direct TSLP administration, TSLP played a crucial role in the well-established OVA/alum asthma model. In this model, TSLP protein was found in the BAL and lung after intranasal OVA

challenge, and disease symptoms were curtailed in the absence of TSLPR or when TSLP activity was blocked by antibody or rTSLPR protein [26, 82–85]. In the OVA mouse model of AR, blocking TSLP also inhibited disease development [86].

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 [7, 42, 87]. Furthermore, multiple studies have shown that the actions of TSLP on DCs were responsible for the disease phenotype observed in mouse models of asthma [26, 81, 83–85]. TSLP-induced DC expression of costimulatory molecules, in particular, OX40L, and DC production of TH2 chemokines, such as CCL17 and CCL21, are likely the predominant mechanisms of action [26, 81]. However, TSLP may also influence the challenge stage of allergic airway disease by supporting TH2 CD4⁺ T cell cytokine production [56, 82–86]. TSLP may also influence the Treg compartment. Several reports have shown the ability of TSLP to promote the development of thymic Tregs in vitro [88]; however, in vivo, its role is unclear. In allergic airway disease, TSLP inhibited IL-10-mediated Treg function and the formation of inducible Tregs to exogenous antigen [89]. Importantly, the BAL fluid from asthmatics inhibited pulmonary Treg function in a TSLP-dependent manner [89]. Additionally, in the OVA asthma model, Nod2 and to a lesser extent, Nod1 stimulation blocked tolerance to OVA intranasal challenge in a TSLP- and OX40L-dependent manner [33]. In this model, loss of TSLP signaling correlated with increased antigen-specific FOXP3⁺ T cells following Nod2 stimulation.

A variety of stimuli, such as IL-4, IL-13, TNF- α , IL-1, bacterial peptidoglycan, lipoteichoic acid, dsRNA, respiratory viruses, air pollutants, and allergens have been shown to induce TSLP expression by lung-derived parenchymal cells and immune cells [7, 11, 42, 52, 63, 87, 90–92]. In particular, stimulation of Nod1 and Nod2 in nonhematopoietic cells was a potent inducer of TH2 immunity via TSLP [93]. These stimuli likely all drive NF- κ B-dependent expression of TSLP, as was shown to occur in human lung epithelial cells [90]. Furthermore, TSLP transcription was negatively regulated by 9-cis-RA via RXRs in lung cells [94]. Exposure to certain infectious agents or repeated environmental irritants may prime production of TSLP, leading to TH2-mediated human disease. For example, even in the absence of known lung disease, lung samples from smokers contained increased TSLP levels as compared with nonsmokers [64]. In addition, lung epithelial cells from asthmatics produced more TSLP in response to dsRNA (viral analog) stimulation in culture [95, 96], which may explain, at least in part, why patients with asthma tend to suffer more airway dysfunction after respiratory infections compared with healthy individuals [97]. This aberrant TSLP production in response to lung insults may thus influence the susceptibility of certain individuals to develop allergic respiratory diseases such as asthma, as well as the clinical complications that arise after environmental insults to the lungs of these individuals.

Collectively, these data illustrate that aberrant lung expression of TSLP is associated with human allergic airway disease and can mimic asthma-like disease in mice. According to genetic studies and in vitro analyses, lung samples from individuals with asthma or COPD produce more TSLP in response to lung insult as compared with samples from healthy individuals. Clinical trials targeting TSLP in these conditions are currently underway. According to mouse asthma models, TSLP appears to influence the sensitization stage of allergic airway responses, but a more in-depth examination of the influence of TSLP on the allergic effector response is required. Where and when TSLP acts during allergic airway disease will likely explain any trial results and dictate future therapeutic design.

Intestinal inflammation

TSLP is constitutively expressed in the mouse and human gastrointestinal tract but can be induced further by a variety of cytokines, microbes, and microbial products [28, 98–103]. Mice carrying gene deletions specifically affecting the gut mucosa provide additional clues into the regulation of TSLP expression within the gut. TSLP mRNA levels were decreased significantly in mice with intestinal epithelial-specific deletion of Dicer [104], an enzyme involved in microRNA biosynthesis, or I κ B kinase- β [99]. Both of these knockout mice showed increased susceptibility to infection with the mouse whipworm *Trichuris muris*. TSLP expression was also decreased in mice carrying a missense mutation in the *Muc2* mucin gene that resulted in an epithelial defect and spontaneous colitis [105]. In in vitro analyses of TSLP intestinal function, human colonic or gastric epithelial-derived TSLP has been implicated in conditioning DCs to drive development of inflammatory TH2 cells [106], Tregs [31], or T cell-independent IgA2 class-switching [28]. Whereas supernatants from human and mouse IECs can condition DCs to drive Treg differentiation, the requirements for TSLP may differ in humans and mice, as the presence of TSLP was required in human but not mouse IEC supernatants to drive a tolerogenic DC phenotype [31, 107]. Additional studies are just beginning to define whether and under what conditions TSLP may function in these pathways in vivo.

As is seen in atopic diseases of the skin and lung, aberrant expression of TSLP was also seen in allergic diseases of the gut. Polymorphisms in TSLP and the TSLPR were associated with the food allergy-related disorder EoE, and this association persisted when comparing EoE patients with allergic individuals without EoE [108, 109]. Additionally, TSLP mRNA expression was higher in the esophagus of pediatric patients with EoE compared with controls and was decreased in homozygotes of the protective GG minor allele for the rs3806932 SNP. Some studies suggest, however, that TSLP not only plays an important role in the promotion of TH2 responses but is also a key player in maintaining intestinal homeostasis and modulation of TH1/TH17 inflammation. In contrast to the increased TSLP expression seen in EoE, decreased TSLP expression was seen in noninflamed colonic tissue in Crohn's disease and UC, the two types of IBD [31, 98, 110, 111]. However, studies of UC have indicated that in inflamed tissue, TSLP expression is up-regulated compared with noninflamed tissue from UC patients or controls [101, 111].

Mouse models of TH2- and TH1-type inflammation also suggest important roles for TSLP in TH2-mediated immunity, main-

tenance of homeostasis, and modulation of TH1/TH17 responses within the gut. TSLP was required to induce diarrheal disease in a mouse model of food allergy [112] and protective TH2 responses to infection with *T. muris* [99]. However, TSLP was not required for oral tolerance to OVA or for anaphylaxis and IL-4, IL-13, and IgE production following intragastric OVA/cholera toxin sensitization and challenge [112]. Additionally, other helminths, such as *Heligmosomoides polygyrus*, *Nippostrongylus brasiliensis*, and *Schistosoma mansoni*, still induced TH2 responses in TSLPR^{-/-} mice, although in some cases, these responses were modified or slightly attenuated [113, 114]. Thus, whereas TSLP may promote TH2 responses in the gut, it is not absolutely required for TH2-type inflammation. In contrast to *T. muris*, *H. polygyrus* and *N. brasiliensis* produce excretory/secretory products that acted on DCs to decrease IL-12/23p40 production. Of note, protective TH2 responses can be induced in *T. muris* infections in the absence of TSLP following the blockade of IFN- γ or IL-12/23p40 [100, 113], suggesting that TSLP may play a prominent role in attenuating TH1 and TH17 responses.

Studies using mouse models of colitis have demonstrated important effects of TSLP in modulating the disease phenotype in intestinal inflammation, although there have been some conflicting results. In a chemical colitis model using DSS, Taylor et al. [100] showed that mice lacking the TSLPR developed more acute weight loss and increased colonic inflammation, which correlated with higher levels of IFN- γ and IL-17A within the mesenteric LNs. In contrast, Reardon et al. [17] reported comparable disease onset and severity in the DSS colitis model between mice that lack TSLP signaling versus controls. However, whereas WT mice recovered after DSS withdrawal, mice lacking TSLP or its receptor had progressive disease and weight loss [17]. Reardon et al. [17] showed that SLPI was induced in DSS colitis in WT mice and that this induction was lost in TSLP^{-/-} mice. NE is a target of SLPI and functions to degrade a number of substrates, including progranulin, a protein important in wound healing. Consistent with a role for TSLP in the inhibition of NE, TSLP^{-/-} mice displayed increased NE activity after treatment with DSS, and inhibition of NE reduced mortality in TSLP^{-/-} mice in this colitis model. Whereas methodological differences may account for some of the discrepancies between these studies, a growing body of evidence demonstrates that differences in microbiota among various facilities can have profound effects on the development and function of the intestinal, as well as systemic, immune system [115]. Thus, further exploration of how the gut microbiota affect TSLP expression and function may be warranted.

These studies support a role for TSLP in the promotion of TH2 responses in the gastrointestinal system but also provide important evidence that TSLP plays a key role in the maintenance of immune homeostasis within the gut. Not only does TSLP function to attenuate TH1/TH17 responses, it also acts directly on the intestinal epithelium to support wound healing in colitis. Whether TSLP also contributes to wound healing and blockade of TH1/TH17 responses at other sites remains to be determined.

Cancer

Recent reports have suggested that TSLP is also associated with breast and pancreatic cancers, which display an increased infiltration of TH2 cells [116–118]. Breast and pancreatic can-

cer cells and cancer-associated fibroblasts have been shown to produce TSLP in response to cancer cell-derived inflammatory cytokines and possibly other unidentified stimuli [116–118]. Furthermore, supernatants from these cells induced DC production of the TH2-attracting chemokines CCL17 and CCL22 and up-regulation of DC costimulatory molecules CD80, CD86, OX40L, and TSLPR in a TSLP-dependent manner. These supernatant-primed DCs were able to promote TH2 polarization of CD4⁺ T cells in vitro. In support of these in vitro data, activated DCs and CCL17 and CCL22 were detected in the tumor and draining LNs but not nondraining LNs of human patients [116]. Importantly, a decreased ratio of TH1/TH2 cells in human pancreatic cancer cases was associated with disease progression and was an independent prognostic marker of reduced survival [116]. Whereas breast cancer cells with intact TSLP expression were able to induce tumor growth and metastasis in mice, short hairpin RNA knockdown of TSLP in these cells resulted in clones with minimal growth or metastasis [117]. Tumor progression and metastasis of an injected breast cancer or melanoma cell line were also decreased in TSLPR-deficient mice compared with WT mice [117].

Previous work has shown that TH2 cytokines promote disease progression through increased survival of cancer cells, M2 macrophage differentiation, and fibrosis (collagen degradation and synthesis) [119–123]. Now TSLP appears to be linked to these phenomena in some human cancers. Alternatively, TSLP may promote tumor progression by controlling Treg migration. CCL22 production in human breast cancer is involved in the influx of tumor Tregs that may then alter the immunoregulatory environment [124, 125]. Further investigation is needed to identify the important sources and targets of TSLP within the tumor environment.

In addition to the association of TSLP with certain solid tumors, the TSLPR has been shown to be overexpressed in 5–10% of childhood B cell progenitor ALL cases and ~60% of ALL cases in children with Down's syndrome [40, 126–128]. Approximately 15% of adult and high-risk pediatric B-ALL cases that lack characteristic rearrangements demonstrated TSLPR overexpression [129]. In almost all cases, TSLPR overexpression was associated with intrachromosomal deletion or rearrangement of the TSLPR/CRLF2 locus with the Ig heavy chain locus, placing TSLPR/CRLF2 under alternate transcriptional control downstream of the P2YR8 promoter [40, 126, 129]. These mutations were highly correlated with the presence of JAK2 mutations and were associated with a poor prognosis [40, 126–131]. In murine Ba/F3 cells, expression of TSLPR and JAK2 mutant alleles promoted growth factor-independent growth [126, 129]. Mice with systemic overexpression of TSLP may provide a model for understanding the signaling mechanisms involved. In particular, loss of keratinocyte-specific Notch signaling resulted in high systemic levels of TSLP, which correlated with a rapid expansion of pre-B cells in the early postnatal period, contributing to early mortality in these animals [51]. Interestingly, overexpression of TSLP early in the postnatal period was sufficient to drive a B cell lymphoproliferative disorder, but administration or induction of TSLP after Postnatal Day 14 was not. However, other studies have shown expansion of B cell compartments following TSLP expression in adult mice [39].

The association of TSLP and TSLP signaling pathways with hematologic malignancies, as well as solid tumors, implicates TSLP/TSLPR in numerous regulatory pathways that support cell growth and survival in cancer. In B-ALL, activation of signaling pathways downstream of TSLP directly promotes the growth and survival of malignant cells, whereas in breast and pancreatic cancer, TSLP likely contributes to multiple components of the tumor environment that affect growth and metastasis, as well as immune evasion. Several reports suggest that TSLP/TSLPR may be useful as a prognostic marker and may present a novel target for therapeutic intervention in cancer.

Other autoimmune diseases and issues of tolerance

Mouse models with constitutive or inducible overexpression of TSLP have demonstrated that TSLP can be associated with autoimmune phenomena. TSLP overexpression in these mice was associated with the development of cryoglobulinemic glomerulonephritis as a result of increased production and kidney deposition of systemic polyclonal IgM and IgG via a monocyte/macrophage-dependent mechanism [39, 132, 133]. In addition, these mice developed red blood cell-specific autoantibodies and autoimmune hemolytic anemia in a CD4⁺ T cell- and IL-4-dependent manner [134]. Whether TSLP is involved in human mixed cryoglobulinemia or autoimmune hemolytic anemia is unknown.

As discussed earlier, TSLP expression was decreased in IBD, a disorder that is thought to arise as a result of inappropriate immune activation against normally harmless microflora. Additionally, loss of TSLP signaling in a mouse model of autoimmune gastritis resulted in more severe disease [135]. Although the impact of TSLP on colitis in mice appears more complex [17, 100], this supports a model in which loss of TSLP, which can block TH1/TH17 responses, leads to increased inflammation. However, data from humans and mouse models suggest that TSLP may actively promote inflammation in TH1/TH17-associated autoimmune diseases, such as RA and MS. In a proteoglycan-induced arthritis mouse model of RA, TSLPR-deficient mice had reduced immunopathology associated with decreased levels of production of IL-17, IL-1 β , and IL-6 but increased IFN- γ and IL-10 [136]. Furthermore, blocking TSLP in a collagen-induced arthritis model ameliorated disease, while administering rTSLP protein exacerbated disease [136, 137]. Increased synovial concentrations of TSLP, as well as TNF- α , have also been seen in synovial fluid from RA patients compared with samples from patients with osteoarthritis. In in vitro studies, TSLP-primed human mDCs induced proliferation of self-reactive CD4⁺ T cells capable of TH1 or TH2 differentiation and TSLP priming of DCs, in conjunction with TLR3 ligand, supported TH17 differentiation [9, 137, 138]. Thus, although the role of TSLP in RA is largely undefined, these data provide intriguing evidence of its possible involvement.

Other autoimmune diseases, specifically MS and type 1 diabetes, have been associated with SNPs in the IL-7R α gene locus and altered Treg numbers or function [139–142]. Although TSLPR pairs with IL-7R α and TSLP can affect Treg development, neither disease has yet been directly linked to TSLP. However, administration of TSLP or TSLP-treated BMDCs into nonobese diabetic mice prevented the development of diabetes in these mice [30], suggesting a possible role

for TSLP in disease therapy. Although the mechanisms involved in protection from diabetes have not been determined, protection was associated with an increased number of Tregs.

One final link that has been made between TSLP and immune tolerance is in maternal-fetal tolerance during pregnancy. TSLP was produced and secreted by first-semester trophoblasts, and tissue from normal pregnancies demonstrated a TH2 bias and higher levels of TSLP expression than samples from miscarriages [143]. Thus, whereas TSLP expression and a TH2 bias may lead to disease progression in cancer, TSLP may contribute to tolerance at the maternal-fetal interface.

CONCLUDING REMARKS

Incredible progress has been made in understanding the cellular changes induced by TSLP during TH2-type inflammation. Multiple cell lineages express the functional TSLPR that helps drive the immune response. More recent data have illustrated that TSLP is also involved in numerous disorders beyond just allergy and may play a role in maintaining homeostasis in diseases, such as IBD, or in disease progression in cancer and autoimmunity. To use the knowledge gained about the biological effects of TSLP, a better understanding of cell-specific signaling pathways must be delineated. Of utmost importance is deciphering whether TSLP invokes similar signaling pathways within different cells. Knowledge of the key targets and sources of TSLP in different disease states will also be important in furthering our comprehension of the pathophysiology of TSLP-associated disorders. Tools that can address these questions, such as approaches that use conditional deletion of the TSLPR and cytokine, will be important in the continued investigation of the role of TSLP during atopic and nonatopic conditions.

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