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Functions of Thymic Stromal Lymphopoietin in Immunity and Disease

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Abstract

Thymic stromal lymphopoietin (TSLP) is an interleukin 7 (IL-7)-like cytokine expressed mainly by epithelial cells. Current studies provide compelling evidence that TSLP is capable of activating dendritic cells (DCs) to promote T helper (Th) 2 immune responses. TSLP has also been shown to directly promote Th2 differentiation of naïve $CD4^+$ T cell, and activate natural killer T (NKT) cells, basophils and other innate immune cells at the initial stage of inflammation. In addition, TSLP affects B cell maturation and activation, and can also influence regulatory T (Treg) cell differentiation and development. TSLP-induced Th2 responses are associated with the pathogenesis of allergic inflammatory diseases, including atopic dermatitis (AD), asthma and rhinitis. Based on recent findings in humans and mouse models, TSLP might also be involved in the pathogenesis of inflammatory bowel disease and progression of cancer. In this review, we will summarize our current understanding of the biology of TSLP, and highlight the important issues for future investigations.

Keywords

TSLP; allergy; Th2; cancer; inflammation

Introduction

The role of the epithelial cells in initiating and regulating immune responses has been increasingly appreciated over the past decade. Epithelium including the skin, the gastrointestinal tract and airways are the initial exposure sites to foreign allergens. The interaction between the epithelial cells and the resident dendritic cells (DCs), as well as other immune cells through epithelial cell-derived cytokines and chemokines, influence the subsequent immunological cascade leading to immunity or diseases. Thymic stromal lymphopoietin (TSLP) is one product of crosstalk produced by the epithelial cells. Due to its well established role as a master regulator of allergic inflammation in humans and mice, TSLP is currently a target of intense investigation. In this review, we will first discuss recent advances in our understanding of the biology of TSLP, including the structure of TSLP and its receptor complex, as well as its signaling pathway. We will also summarize the cellular targets of TSLP, such as DCs, lymphocytes and innate immune cells. Finally, we will focus

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Disclosures

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on the effects of TSLP on the development of diseases, including allergic inflammation, and discuss TSLP as an attractive therapeutic target for allergic diseases and cancers.

Discovery of TSLP

TSLP was originally discovered in conditioned media of a phenotypically unique thymic stromal cell clone, Z210R.1, which supported the development of immature NAG8/7 B cells to more mature $B220^+/IgM^+$ stage and enhanced the proliferation of unfractionated thymocytes to suboptimal concentrations of anti-CD3 antibodies in vitro [1]. From a Z210R.1 expression library, TSLP cDNA was isolated by direct expression screening [2]. The expressed TSLP protein, shared an overlapping but distinct biological profile with IL-7. Both cytokines promote the maturation of B lymphocytes in long-term cultures of fetal liver cells and bone marrow (BM), with TSLP apparently supporting progression to more mature $B220^+IgM^+$ stages than IL-7, which promotes development only to an IgM^- stage [1, 3, 4]. Furthermore, murine $B220^+IgM^-$ BM cells differentiate into IgM^+ cells after 7 days of culture with TSLP [2].

The mouse TSLP protein has a 140 amino acid single open reading frame, including a predicted 19–amino acid signal peptide. The mature 121–amino acid mouse TSLP protein contains 3 potential sites for N-linked carbohydrate addition and 7 cysteine residues, which could potentially form as many as three disulfide bonds [2]. The human homologue of murine TSLP was subsequently identified [5, 6]. Murine *Tslp* is mapped to chromosome 18, while human *TSLP* is located on chromosome 5q22.1, centromeric to the atopic cytokine cluster on 5q31 [2, 5].

Regulation of TSLP expression

TSLP is a misnomer, and is primarily expressed by epithelial cells lining the skin and mucosal surfaces of airways and intestines [6]. NF-κB binding sites were identified in both human and mouse TSLP promoter [7, 8], and TSLP expression in human airway epithelial cells was regulated by proinflammatory mediators, IL-1β and tumor necrosis factor (TNF)-α, in a NF-κB dependent manner [7]. Although proinflammatory (TNF-α or IL-1α) alone did not stimulate significant amounts of TSLP in human skin explant, they, in synergy with Th2 cytokines, induced TSLP sufficient to promote maturation of blood $CD11c^+$ DCs [9]. Given the critical role of NF-κB downstream of Toll-like receptors (TLR) signaling pathways, it was not surprising that various TLR agonists, as well as infections, stimulated TSLP expression in epithelial cells [7, 10-20].

Unrestrained serine protease activity in skin leads to upregulation of TSLP. Netherton syndrome (NS) is a genetic skin disease with severe atopic manifestations including recurrent atopic dermatitis, higher IgE concentrations, asthma and multiple food allergies. Genetic defects of the serine protease inhibitor Kazal-type 5 (SPINK5) in NS resulted in uncontrolled epidermal serine protease kallikrein 5 (KLK5) activity, which in turn activated proteinase-activated receptor 2 (PAR2) and induced nuclear factor NF-κB-mediated overexpression of TSLP [21, 22]. Likewise, knockdown of the transcription factor Specificity protein 1 (Sp1) expression in normal human keratinocytes led to upregulation of six kallikrein-related protease genes KLK5, KLK6, KLK7, KLK8, KLK10, and KLK12. Elevated KLK activity in Sp1-silenced keratinocytes induced TSLP expression [23].

In addition to NF-κB, nuclear receptors including vitamin D receptor (VDR) and retinoic X receptor (RXR) have been reported to regulate TSLP expression in epithelial cells [8]. Putative nuclear receptor response elements were identified in both human and mouse TSLP promoter, and topical application of vitamin D3 and its low-calcemic analog MC903 induced high expression of TSLP in keratinocytes. Keratinocyte selective ablation of RXRα

and RXRβ in mice led to TSLP expression and development of chronic skin inflammation [24]. Consistent to these results, 9-*cis*-retinoic acid blocked recruitment of NF-κB to the human TSLP promoter thus inhibited IL-1β-mediated TSLP expression in human airway epithelial cells [25].

The RNase III enzyme Dicer is essential for processing pre-miRNAs into mature, functional miRNAs, which are capable of post-transcriptional gene regulation by binding to their target mRNAs, leading to mRNA degradation or/and suppression of translation. Using Dicer mutant mice with induced ablation of Dicer in epidermal KCs [26], keratinocytic miRNA was implicated in the pathogenesis of AD by regulating TSLP. The involvement of miRNAs in modulating TSLP expression was also found in gut epithelium in that IL-13-induced miR-375 upregulated TSLP and knockdown of miR-375 abolished TSLP induction [27].

Proinflammatory cytokines IL-1β and TNF-α stimulated human airway smooth muscle cells to express TSLP [28]. This upregulation of TSLP was dependent on not only NF-κB and AP-1 transcription factors [29], but also p38 and p42/44 (ERK) MAP kinase signaling pathways, as pharmacological suppression of these MAP kinases but not PI3 kinase, significantly decreases in TSLP release on IL-1β and TNF-α treatment [28].

As we will summarize below, DCs are the major target of TSLP. Unexpectedly, both human and mouse DCs also produced TSLP in response to TLR stimulation [30]. The function of DC-derived TSLP remains an enigma. In a low LPS induced allergic airway inflammation model, we found that DC-derived TSLP played a critical role in priming Th2 sensitization. While adoptive transfer of low LPS + OVA conditioned wild type DCs induced Th2 responses with airway eosinophilia, transfer of low LPS + OVA conditioned TSLP-deficient DCs resulted in Th1 responses with airway neutrophilia (Zhang and Zhou, unpublished data). Thus, DC-produced TSLP may be relevant in T cell programming.

TSLP signaling pathway

TSLP receptor (TSLPR) which binds TSLP with low affinity is a member of the hematopoietin receptor family [31]. A combination of IL-7 receptor α chain (IL-7Rα) and TSLPR is required for high affinity binding of TSLP, cell proliferation, and activation of STAT5 [3, 6, 32]. The γ_c chain which is common to IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptor complexes [33, 34] is not required for TSLP binding and function [3].

TSLP is capable of inducing the phosphorylation of Stat5 in pre-B cell line (NAG8/7). Although initial results suggested that TSLP engagement on TSLPR complex activated STAT5 without detectable JAK activation. [3, 35], recent results using primary mouse and human $CD4^+$ T cells demonstrated that JAK1 and JAK2, which bind to IL-7Rα and TSLPR chain respectively, is required for TSLP-mediated STAT5 activation [36].

In human myeloid DCs (mDCs), TSLP induced phosphorylation and activation of all known STATs except for STAT2 likely through robust and prolonged activation of JAK1 and JAK2 [37].TSLP-activated pSTAT6 binds to the promoter of Th2-attracting chemokine gene *CCL17* [37], suggesting a molecular mechanism of TSLP-mediated CCL17 induction in human mDCs [38]. In addition to STATs phosphorylation, TSLP also induced sustained activation of NF-kB molecules p50 and RelB, which bound to and thus might be responsible for the activation of the *OX40L* promoter in TSLP activated myeloid DCs [37]. In mouse $CD4^+$ T cells, activation of Stat5 by TSLP could direct the initial IL-4 production independent of IL-2 [39].

Cellular targets of TSLP

TSLP is expressed predominantly by epithelial cells in the thymus, lung, skin, intestine, and tonsils as well as stromal cells and mast cells but is not found in most hematopoietic cell types and endothelial cells [5, 38, 40]. In contrast, TSLP receptor (TSLPR) has been found on DCs, T cells, B cells, mast cells, NKT cells, and monocytes as well as tissues from heart, skeletal muscle, kidney, and liver [6, 31, 32]. Indeed, as reviewed below, TSLP exerts its functions on a broad range of tissue and cell types.

Dendritic cells

Monocytes and dendritic cell populations are known to have the highest co-expression of human TSLPR and IL-7Rα [6]. TSLP has the capacity to potently enhance the maturation and function of $CD11c^+$ human myeloid DCs, as evidenced by the strong induction of the MHC II, costimulatory molecules CD40 and CD80, and release of Th2 cell-attracting chemokines [6, 38]. Similarly, murine bone marrow–derives DCs responded to TSLP treatment by producing chemokine CCL17 and increasing MHC II and costimulatory protein expression [41].

TSLP produced by epithelial cells or keratinocytes can skew the developing immune response toward a proallergic state through its direct action on DCs. This concept is supported by studies showing that TSLP can directly activate DCs to express OX40L to prime naive $CD4^+$ T cells to differentiate into proinflammatory Th2 cells characterized by high amounts of IL-4, -5, -13 and TNF-α, but no IL-10 and IFN-γ [38, 42]. Analysis of microarray experiments on TSLP-activated human blood $CD11c^+$ DCs have shown that TNF superfamily protein OX40L was strongly induced by TSLP [42]. *In vivo* studies also demonstrated TSLP induced Th2 inflammation was mediated by OX40-OX40L interaction. Treating mice with OX40L-blocking antibodies substantially inhibited TSLP-induced immune responses in the lung and skin, and also inhibited antigen-driven Th2 inflammation in mouse and non-human primate models of asthma, including Th2 inflammatory cell infiltration and cytokine secretion [43].

TSLP activated DCs (TSLP-DCs) play crucial roles not only in Th2 priming, but also in the maintenance and expansion of Th2 central memory cells expressing the prostaglandin D2 receptor CRTH2 [44]. While $CRTH2^+CD4^+$ Th2 central memory (T_{CM}) cells cultured with IL-15 plus IL-7 or anti-CD3/CD28 lost the expression of T_{CM} marker CCR7 and CD27, TSLP-treated DCs supported Th2 T_{CM} to maintain expression of CRTH2/CCR7/CD27/CD62L and the Th2 cytokines IL-4/IL-5/IL-13. Again, OX40L expressed by TSLP-DCs was required for prolonged DC-T cognate formation and contributed to drive the homeostatic proliferation of Th2 memory cells [44].

TSLP acting through DCs can profoundly modulate Th1/Th2 immune responses. Human TSLP primed DCs produced high levels of IL-12 followed by CD40L stimulation [45]. However, TSLP/CD40L DCs still conserved their ability to prime Th2 differentiation so that naive $CD4^+$ T cells polarized by TSLP/CD40L DCs produced both Th1 and Th2 cytokines. TSLP thus may contribute to create a permissive microenvironment leading to the maintenance of the Th2 phenotype even in the presence of high level of IL-12 [45]. Intestinal epithelial cells (IECs)-derived TSLP modulates gut mucosal immunity as well. Monoclonal antibody-mediated neutralization of TSLP or deficiency of TSLPR in normally resistant mice resulted in susceptibility to *Trichuris* [46]. Mice with an IEC-specific deletion of IKKβ have impaired expression of TSLP and failure to mount protective Th2-type responses following *Trichuris muris* infection [47]. In both cases, lack of TSLP signaling resulted in decreased Th2 cytokines and increased expression of IL-12/23p40, IFN-γ, and IL-17A.

In addition to affecting T helper differentiation, human TSLP-treated $CD11c^+$ DCs potently activated and expand naive $CD8^+$T cells, and induced their differentiation into IL-5 and IL-13-producing effectors with poor cytolytic ability. Addition of CD40L to TSLP-activated DCs could induce large amounts of IFN-γ and potent cytotoxicity by $CD8^+$ T cells while retaining their capacity to produce IL-5 and IL-13 [48]. These IL-5, IL-13, and IFN-γ-producing cytolytic effectors might amplify and maintain the pro-allergic response, and further induce tissue damage by promoting the generation of IFN-γ producing cytotoxic effectors.

TSLP induced the release of a proliferation-inducing ligand (APRIL) by intestinal epithelial cells (IEC)-conditioned mucosal DCs, and amplified IEC-induced IgA class switching in humans after TLR stimulation of IECs [49]. Similarly, epithelial cells lining tonsillar crypts produced TSLP which in turn induced BAFF production by DCs to amplify local concentrations of BAFF and potentiate its effect on naive B cell class switching to IgG and IgA [50].

T cells

Although TSLPR-deficient mice exhibited normal lymphohematopoietic development [51, 52], TSLP preferentially stimulated the proliferation and survival of CD4 single positive thymocytes and peripheral T cells in vitro. When transferred into irradiated hosts, $CD4^+$ T cells from *Tslpr*$^{-/-}$ mice expanded less efficiently than WT $CD4^+$ T cells, suggesting a direct effect of TSLP on $CD4^+$ T cell homeostasis [51]. Furthermore, activation and proliferation of TSLPR-deficient $CD4^+$ T cells was much weaker than wild type cells after immunization as well as secondary exposure to the antigen [53].

Conflicting results were reported concerning the direct effects of TSLP on human $CD4^+$ T cells. Human TSLP was shown to stimulate STAT5 phosphorylation in $CD4^+$ T cells [36, 54, 55] and TSLP treatment increased proliferation of TCR-activated $CD4^+$ T cells [55]. However, in a study of late phase cutaneous responses, human T cells from a limited number of healthy subjects don't express a functional TSLPR [56] and human T cells fail to response to TSLP *in vitro* [57]. Even though $CD4^+$ T cells upregulated TSLPR expression after TCR activation [55, 58], its expression level was rather low compared to that expressed by mDCs [54]. Furthermore, TSLP only marginally improved $CD4^+$ T cell survival and proliferation, but failed to induce cell expansion and Th2 differentiation [54].

In the mouse model, results appear more consistent with TSLP having direct effects on T cells. TSLP treatment of naïve $CD4^+$ T cells, following TCR stimulation, resulted in immediate *Il4* gene transcription and Th2 differentiation in the absence of antigen-presenting cells (APCs) and exogenous IL-4 [39, 58]. Consistent to the notion that IL-4 plays a critical role in priming naïve $CD4^+$ T cells into Th2 cells [59], the ability of TSLP to promote Th2 differentiation relied on endogenous IL-4 expression by the $CD4^+$ T cells and activation of Stat6 [39]. In a papain-induced asthma model, TSLP released by activated basophils was found to promote Th2 differentiation *in vivo* [60]. In a model of allergic skin inflammation, TSLP might not be important for the recruitment and accumulation of T cells, or DC maturation and activation, but was essential for skin infiltrating effector $CD4^+$ T cells to amplify Th2 cytokine secretion under local antigen stimulation [61]. Mouse Th2 cells expressed relatively higher TSLPR than other Th subsets and TSLP induced proliferation of Th2 cells, but not Th1 and Th17 cells [62].

In addition to $CD4^+$ T cells, TSLP has also been demonstrated to act on $CD8^+$ T cells. It is well known that IL-7Rα expression is strongly required for human and mouse $CD8^+$ T cell survival and homeostatic proliferation under lymphopenic conditions [63, 64]. Both TSLPR and IL-7Rα are expressed by $CD8^+$ T cells, and TSLP could directly act on human and

mouse $CD8^+$ T cells to activate the STAT5 and Akt signaling pathways in these cells [65]. *In vitro*, TSLP served as a survival factor for $CD8^+$ T cells through upregulating the expression of Bcl-2 [65], the same mechanism thought to be important in IL-7-mediated survival of T cells [66]. However, unlike IL-7 which sustained both proliferation and survival of $CD8^+$ cells, TSLP only increased their survival without altering the homeostatic proliferation of these cells [65].

B cells

The primary organs of mouse B lymphocyte production happens are the fetal liver and the adult bone marrow [67]. Lymphopoiesis is regulated by a number of cytokines that control the proliferation, differentiation, and survival of hematopoietic progenitor cells [68, 69]. TSLP was originally identified as a cytokine that supported *in vitro* development of B cell precursors from day-15 fetal liver and long-term bone marrow culture [1, 3, 4] to IgM^+ stage after successful rearrangement of the heavy chain locus.

BM lymphoid and myeloid progenitors as well as DN thymocytes are responsive to TSLP. In $Il7^{-/-}$ K14-TSLP Tg mice, TSLP fully restored central and peripheral lymphoid compartments and amplified myeloid cells in the periphery [70]. Overexpression of TSLP resulted in preferential population expansion of peritoneal B-1b B cells and follicular mature B cells, but near-complete loss of marginal zone and marginal zone precursor B cells [71]. However, there are some discrepant results on the role of TSLP overexpression on B cell lymphopoiesis *in vivo*. Murine TSLP provides no essential support for B-cell development when examining $Tslpr^{-/-}$ mice [51, 52], while TSLP transgene expression resulted in either promoted [71] or inhibited B lymphopoiesis [72]. The explanation of these conflicting results remains enigmatic at present. It might be a result of different circulating levels of TSLP which influences the frequency and composition of B-cell populations *in vivo*, which is supported by the observation that a large amount of TSLP, released into systemic circulation by Notch-deficient keratinocytes (KCs) during neonatal hematopoiesis, induced drastic expansion of peripheral pre- and immature B-lymphocytes, causing B-lymphoproliferative disorder and further death [73].

$Il7r^{-/-}$ mice have 1% the number of B cells of controls, while $\gamma_c{}^{-/-}$ mice have 10% of control B cell numbers. Since TSLP and IL-7 receptors share the IL-7Rα subunit but not the γ_c chain, the difference between IL-7Rα- and γ_c-deficient mice supported a role for TSLP in fetal and perinatal lymphopoiesis independent of IL-7 [74]. Pre-B cells from both fetal liver and bone marrow were responsive to TSLP, although the bone marrow pre-B cells also required pre-B cell receptor expression to be responsive [75]. Surprisingly, only fetal-derived pro-B cells were able to respond to TSLP despite the same expression levels of TSLPR, γ_c and IL-7Rα were found on pro-B cells from both origins [74].

Innate immune cells

Th2 cytokine-mediated allergic responses are orchestrated by both innate and adaptive immune cells. In addition to DCs and T cells, innate immune cells, including NKT cells, mast cells, eosinophils and basophils are also cellular targets of TSLP. TSLP directly acted on NKT cells, which express TSLPR as well as IL-7Rα, to produce IL-13. In an allergen-induced asthma model, increased airway hyperreactivity was not observed in TSLP transgenic mice lacking NKT cells while airway eosinophilia and IgE levels were similar to the mice with NKT cells [76]. Likewise, human eosinophils also constitutively express functional TSLP receptors. TSLP significantly delayed eosinophil apoptosis, and upregulated cell surface expression of the adhesion molecules CD18 and ICAM-1 through ERK-, p38 MAPK-, and NF-κB-dependent, but STAT3- and STAT5-independent signaling pathways [77]. The inflammatory infiltrate in the dermis of K5-TSLP or MC903-treated

mice contained abundant mast cells and eosinophils [8, 78], in the absence of increased serum IgE, suggesting TSLP was able to induce AD-like pathology by stimulating and recruiting mast cells and eosinophils independent of adaptive immune responses. In synergy with IL-1 and TNF, epithelial cell-derived TSLP was sufficient to induce the production of high levels of Th2 cytokines by human mast cells [20]. Furthermore, TNF released by activated mast cells triggered human bronchial smooth muscle cells to express TSLP which in turn activated mast cells in the presence of IL-1 to release Th2 cytokines [79], suggesting a positive loop to amplify Th2 inflammation in chronic asthma. TSLP also promoted basophils to interact with $CD4^+$ T cells in MHC II-dependent way to induce parasite-specific Th2 cytokine responses and host protective immunity to helminth infection [80]. TSLP acted directly on bone-marrow resident progenitors to promote basophil responses selectively in an IL-3 independent manner [81]. TSLP-elicited basophils and IL-3-elicited basophils were functionally different. Basophils isolated from wild type mice and adoptively transferred into normally susceptible *Trichuris*-infected TSLPR-deficient mice were sufficient to restore Th2 cytokine responses [81]. Collectively, the above studies coupled with the critical role of TSLP-TSLPR interactions for immunity to the intestinal pathogen *Trichuris* [46, 82] suggest that TSLP can promote the recruitment of granulocytes like bone marrow-derived basophils to some inflammatory sites where antigen is present, and aid DCs in the initiation of helminth- or allergen-induced Th2 cytokine responses [80, 81, 83].

Regulatory T cells

In addition to promoting Th2 differentiation, TSLP acting through DCs promoted the differentiation and development of regulatory T cells (Tregs) in several cases. In mouse embryonic day 17 fetal thymus organ culture, TSLP treatment enhanced expression of Foxp3, whereas blocking TSLPR results in reduced Foxp3 expression [84]. In human thymus, TSLP released by ECs of the Hassall's corpuscles primed thymic $CD11c^+$ DCs [85] and plasmacytoid DCs (pDCs) [86] to induce the proliferation and differentiation of $CD4^+CD8^-CD25^-$ thymic T cells into $CD4^+CD25^+FOXP3^+$ Tregs. Bone marrow DCs of non-obese diabetic (NOD) mouse cultured with TSLP could be educated into tolerogenic DCs with no expression of pro-inflammatory cytokines and decreased expression of costimulatory molecules. These TSLP-DCs then promoted Treg differentiation and noninflammatory Th2 cells producing IL-10 to protect NOD mice against Type I diabetes [87].

TSLP was also reported to act directly on CD4 single positive thymocytes to promote Treg differentiation [88]. Despite these effects, it is unlikely that TSLP is absolutely required for Treg development. Animals deficient for TSLPR had relatively normal Treg development [89]. However, mice deficient for IL-7Rα or IL-7 and TSLPR double mutant showed greatly reduced Treg development in thymus but no effects on survival of mature peripheral Tregs, suggesting IL-7 and TSLP acting redundantly in thymic Treg development [89]. DCs purified from the lamina propria (LpDCs) of the small intestine promoted a relatively high percentage of Treg cells. This enhanced conversion of Tregs by LpDCs was independent of TSLP as similar frequency and absolute number of Tregs were induced by LpDCs from *Tslpr*$^{-/-}$ and WT mice [90].

Various Th polarizing cytokines such as IL-4, IL-6, IL-12, and IFN-γ are able to suppress the generation of Foxp3-expressing iTregs [91, 92]. We have recently showed that TSLP acted directly on $CD4^+$ T cells to divert airway tolerance against harmless antigen OVA to Th2 sensitization and inhibited the generation of both human and mouse induced Tregs (iTregs) [58]. Even low amounts of systemic TSLP that were unable to promote Th2 differentiation could significantly inhibit the induction of iTreg, indicating that these two functions of TSLP were separable. Furthermore, TSLP-mediated inhibition of iTreg generation was only partially dependent on IL-4 and Stat6 [58].

In human allergic asthma, pulmonary Tregs exhibited a significant decrease in suppressive activity and IL-10 production. Elevated pulmonary TSLP directly impaired Treg function as allergic asthmatic bronchoalveolar lavage fluid could suppress IL-10 production and regulatory funtion by healthy control pulmonary Treg in a TSLP-dependent manner [93].

TSLP in allergic diseases

Atopic dermatitis

TSLP was highly expressed by keratinocytes in the skin lesions of patients with AD [38, 56]. It contributes to the initiation of allergic inflammation by stimulating activation and migration of Langerhans cells into skin draining lymph nodes [38]. TSLP was also essential for local antigen-driven Th2 cytokine secretion by directly acting on skin infiltrating antigen-specific $CD4^+$ T cells [61]. A link between TSLP expression and the pathogenesis of AD has been shown in several mouse models. Skin-specific TSLP-transgenic mice developed an inflammatory skin disease resembling atopic dermatitis [78]. Likewise, aberrant skin TSLP expression in mice with keratinocyte-selective ablation of retinoid X receptors (RXRα and RXRβ) [24] or keratinocyte-specific deletion of total Notch signaling [73, 94] developed a chronic dermatitis syndrome similar to that observed in AD patients. Keratinocytic TSLP expression was attributed to the development of AD-like disease induced by topical application of low-calcemic analog of vitamin D3 (MC903; calcipotriol) [8] since $Tslp^{epi-/-}$ mice, in which TSLP was ablated selectively in KCs, failed to develop skin inflammation [95]. Upon MC903 treatment, mice with induced ablation of Dicer in epidermal keratinocytes showed further increased TSLP expression accompanied with aggravated skin inflammation [26]. Consistent with a requirement for TSLP in allergic skin inflammation, epicutaneously sensitized and challenged $Tslpr^{-/-}$ mice showed greatly reduced allergic skin inflammation compared with WT mice, with decreased number of eosinophils and decreased local expression of Th2 cytokines in the skin [61].

Allergic asthma

Using *in situ* hybridization, Ying et al. reported that the numbers of cells within the bronchial epithelium and submucosa expressing *TSLP* were significantly increased in asthmatics [96, 97]. TSLP protein levels were also found to be elevated in the airway epithelium and BALF of asthma patients [93, 97-99]. Recently, several genome wide association studies in different populations identified that *TSLP* as a susceptibility loci associated with asthma risk [100, 101]. Association studies between *TSLP* polymorphisms and allergic phenotypes showed that several SNPs were associated with asthma risk [102-106]. For example, the A allele of rs1837253 was associated with protection from asthma, atopic asthma, and airway hyperresponsiveness [102, 103], while the T allele of the rs2289276 was associated with lower levels of cockroach allergen-specific IgE and total IgE in girls [107]. TSLP promoter polymorphisms rs3806933 and rs2289276 were significantly associated with disease susceptibility in both childhood atopic and adult asthma, while rs2289278 was correlated with pulmonary function. The polymorphism at rs2289276 altered the affinity of the transcription factor AP-2a with diminished binding ability by the T allele compared with the C allele [106]. The SNP rs1898671 was associated with asthma susceptibility especially in a subgroup of ex-smokers [104]. Significant associations were also noted with a lower FEV_1% predicted and with a lower FEV_1/FVC at SNPs rs3806933 and rs2289276 [105]. The haplotype most strongly associated with lower FEV_1/FVC was rs3806933C/rs2289276C/rs2289278C.

TSLP expression was also increased in the lungs of mice with allergic airway inflammation [41, 108, 109], and TSLPR-deficient mice failed to develop asthma-like disease in OVA sensitized and challenged mice [41, 53]. Blockade of TSLP using TSLPR-Fc fusion protein

[53, 110] or local application of TSLPR-blocking antibody [109] displayed reduced allergic airway inflammatory responses. In contrast, lung-specific expression of TSLP under the control of the surfactant protein C promoter induced airway inflammation and hyperreactivity resembling asthma with increased Th2 cytokines and serum IgE [41].

Although lung-specific TSLP transgenic mice developed spontaneous airway inflammation [41], TSLP per se did not induce airway inflammation but conditioned lung immune environment for antigen-specific Th2 responses against foreign antigens [111]. Furthermore, the lung-specific TSLP transgene failed to induce airway inflammation in mice deficient for IL-4 and Stat6, and blockade of both IL-4 and IL-13 signaling through administration of an anti-IL-4Rα mAb reversed asthma-like symptoms in these mice [112].

Allergic rhinitis and nasal polypsis

Allergic rhinitis is another common allergic disease, together with atopic dermatitis and asthma make up the “allergic triad”. Similar to data from atopic dermatitis and asthma, TSLP is also important for the pathogenesis of allergic rhinitis. Expression of TSLP by the nasal epithelial cells was significantly higher in allergic rhinitis patients than in healthy controls [113-115]. TSLP level present in homogenized nasal tissue biopsies was tightly correlated with IL-4 concentration and severity of AR [113]. Genetic association studies demonstrated that a *TSLP* polymorphism was associated with allergic rhinitis in children with asthma in three independent cohorts from Costa Rican, North America and Sweden [116]. In a mouse model of allergic rhinitis, TSLP was up-regulated predominantly in the nasal epithelium, while administration of neutralizing TSLP antibody during the challenge phase inhibited the development of allergic rhinitis [117].

Nasal polyposis is a chronic inflammatory disease of the upper airways often associated with asthma and rhinitis. TSLP was highly expressed in nasal polyps regardless of their atopic status with highest expression seen in samples from atopic patients and allergic rhinitis patients [115, 118]. The high expression of TSLP was strongly correlated to eosinophil counts and IgE levels in nasal polyps, suggesting a potential role for TSLP in the pathogenesis of nasal polyps by regulating eosinophilic inflammation [115]. In support of this notion, higher TSLPR and OX40L were seen in DCs from nasal polyps. Upregulation of TSLPR and OX40L by peripheral mononuclear cell-derived DCs cultured with nasal epithelial protein extracted from nasal polyp scrapping was inhibited by including neutralizing anti-TSLP antibody in the culture [118].

Eosinophilic esophagitis

Eosinophilic esophagitis (EE) is a severe chronic Th2-associated inflammatory disease of the esophagus characterized by an accumulation of eosinophils in the esophageal mucosa. A high rate of atopic diseases is found in both pediatric and adult EE patients [119, 120]. Food antigen sensitization plays an important role in disease etiology [121]. A multi-center genome-wide association study (GWAS) has identified *TSLP* gene as an important candidate gene in the pathogenesis of EE and an increased expression of TSLP in the esophagi of patients with EE compared with healthy controls [122]. A recent study using customized SNP array in 53 genes implicated in allergy, *TSLP* variants were significantly associated with EE when compared with atopic controls. Furthermore, a genetic variant in *TSLPR* also contributed to EE susceptibility [123].

TSLP and inflammatory bowel diseases

Dysregulated TSLP expression in intestinal epithelial cells (IEC) might be crucial to the pathogenesis of inflammatory bowel disease. Colonic epithelial cells from healthy donors constitutively expressed TSLP resulting in the induction of ‘non-inflammatory’ dendritic

cells which favored non-inflammatory Th2 responses even after exposure to a Th1-inducing pathogen [40]. In fact, human IEC-produced TSLP might be involved in directing monocyte-derived DCs to become tolerogenic DCs in concert with other IEC-derived factors TGF-β and retinoic acid [124, 125]. At another level of control, IECs isolated from nearly 70% of Crohn's disease patients did not express TSLP and failed to control inflammatory responses in the gut [40, 124].

IEC-derived TSLP suppressed DCs production of IL-12/p40, and elevated IL-12/p40 expression in TSLPR-deficient mice led to increased IFN-γ expression and more severe intestinal inflammation in a mouse model of colitis induced by dextran sodium sulfate [46]. Similarly, in an autoimmune gastritis model, TSLPR-deficient mice showed earlier onset and enhanced severity of inflammation with increased autoantibody, IL-12 and IFN-γ [126]. However, using TSLP-deficient mice, a more recent study demonstrated that these mice did not exhibit increased inflammation during dextran sodium sulfate- and $CD4^+CD45RB^{hi}$ T cell transfer-induced colitis, but rather failed to recover from disease due to reduced expression of a TSLP-inducible endogenous inhibitor, Secretory leukocyte peptidase inhibitor (SLPI) [127]. TSLP acted directly on IEC to stimulate SLPI expression with no involvement of Th1 or Th17 cells and their effector cytokines.

TSLP and cancers

Despite its well-known importance in allergic responses, the roles of TSLP in cancer have only recently been identified. It is known that inflammation plays critical roles at different stages of tumor development [128, 129]. While presence of IFN-γ activated macrophages (M1) trigger cancer cell destruction, Th2 cytokine IL-4 and IL-13 activated macrophages (M2) and chronic inflammation promote cancer cell survival and metastasis [130]. TSLP, produced by human breast cancer cells, induced expression of OX40L on DCs which amplified inflammatory Th2 cell differentiation in primary breast tumor infiltrations to produce IL-13 and TNF *in vitro*. Antibodies neutralizing TSLP or OX40L inhibited breast tumor growth and IL-13 production in a xenograft model. Thus TSLP contributes to a Th2 inflammatory microenvironment that promotes breast cancer development [131]. TSLP plays a central role in human pancreatic cancer characterized by predominantly Th2 infiltration. Tumor-derived TNF-α and IL-1β activated cancer-associated fibroblasts to release TSLP, which in turn induced DCs to upregulate TSLPR and acquire Th2-polarizing capability. $CD11c^+TSLPR^+$ DC are present *in vivo* in the tumor stroma and tumor-draining lymph nodes [132].

TSLP is abundantly expressed in various cancers, including human breast cancer and melanoma cell lines and human metastatic breast cancer biopsy [131, 133]. In mice, TSLP expression among different clones of mouse 4T1 adenocarcinoma strongly correlated with tumor progression and metastasis, and knockdown of TSLP expression in cancer cells alone was sufficient to almost completely abrogate cancer progression and lung metastasis. Tumor growth and metastasis were significantly suppressed when 4T1 adenocarcinoma and B16 melanoma were implanted into TSLPR-deficient mice. TSLP, signaling through the TSLPR on $CD4^+$ T cells, played an essential role in cancer growth by promoting Th2-skewed immune responses [133].

Tregs, which suppress immune responses against foreign- and self-antigens and could help the tumor cells to escape the host immune surveillance, were often increased in the peripheral blood, tumor-draining lymph nodes, and tumor microenvironment in cancer patients [134]. Interestingly, the number of Tregs in tumor microenvironment was correlated with the expression of TSLP in lung cancer tissues [135]. DCs derived from PBMC collected from lung cancer patients showed less mature characteristics upon TSLP

stimulation, expressing low levels of IL-6, IL-12, IL-10, TNF-α and IFN-γ, and high levels of TGF-β and MDC. When co-cultured with $CD4^+CD25^-$ T cells, TSLP-activated DCs induced and attracted significantly higher Tregs than LPS-maturated DCs and immature DCs [135], suggesting cancer cell-derived TSLP acting through DCs may contribute to increased Tregs in lung cancer tissues.

TSLP in infection

Given its importance in inducing Th2 differentiation and allergic responses, it is logical to assume a role for TSLP in immunity against parasitic worm helminths. Surprisingly, the requirement of TSLP in helminth immunity is determined by helminth species. For *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis*, TSLP was dispensable for the development of protective immune responses with normal Th2 cell differentiation, protective immunity and memory responses against these two parasites by TSLPR-deficient mice [82]. TSLP also played a limited role in immune responses against *Schistosoma mansoni* [136]; a modest reduction in Th2 cytokines and tissue eosinophilia in acutely infected TSLPR-deficient mice had no effects on granuloma formation or fibrosis in chronic infection. However, TSLP was shown to be required for the development of protective Th2 response against *Trichuris muris* [46, 47, 81, 82]. TSLP inhibited IL-12p40 production in response to *T. muris* infection to suppress Th1 response. TSLPR deficiency led to impaired protective Th2 responses with elevated expression of IL-12p40, IFN-γ and IL-17A accompanied by severe intestinal inflammation [46, 82]. TSLP could also act on basophils to promote Th2 immunity therefore adoptive transfer TSLP-induced wild type basophils into TSLPR-deficient mice was sufficient to recover Th2 cell-dependent immunity to helminth infection [81].

The roles of TSLP in anti-viral infection are unclear. Viral infection of airway epithelial cells [11] and keratinocytes [12] induced TSLP expression. Similarly, TLR agonists associated with viral infection, such as double strand RNA, induced TSLP expression by epithelial cells [7, 13, 19, 20]. Airway epithelial cell-derived TSLP after respiratory syncytial virus (RSV) infection was responsible for activation and functional maturation of DCs displaying increased level of MHC II, OX40L and CD86 [11]. Although the relationship between the pro-Th2 activity and anti-viral immune responses mediated by TSLP was not clear, these findings did provide an interesting link between viral infection, especially RSV infection, and development of wheezing and subsequent asthma in infants and asthma exacerbations in affected people [137].

Concluding remarks

We have learned a great deal about the biological functions of TSLP since this cytokine was cloned more than ten years ago. The role of TSLP in allergic inflammation is currently an area of intense investigation. Building on knowledge gained thus far, TSLP is extremely important in Th2 responses by acting on myeloid and lymphoid populations to coordinate innate and adaptive immunity. Therefore TSLP holds promise as a novel therapeutic target for asthma and other allergic diseases. In addition to reports showing significantly reduced allergic inflammation in TSLPR-deficient mice [41, 53, 61], neutralization of TSLP by antibody or TSLPR-Fc fusion protein also protected mice from developing allergic inflammation [53, 108, 110, 117, 138]. One caveat of these studies is the use of acute allergic models. The fact that proinflammatory cytokines IL-1 and TNF-α, especially in synergy with Th2 cytokines, induced TSLP in epithelial cells and airway smooth muscles [9, 28] suggests TSLP could be a component in a positive feedback loop to maintain chronic inflammation. The efficacies of blocking TSLP and/or TSLP signaling pathway to treat established chronic diseases needs to be tested.

Allergic asthma frequently affects individuals with a prior history of AD. The mechanism underlying the progression from AD to asthma, the so-called “atopic march”, remains unclear. Recent studies showed that keratinocytes of mice with severe AD-like skin inflammation released large amount of TSLP into circulation [139, 140]. It was the systemic TSLP, not the skin lesion per se, that was shown to be responsible for augmenting allergic airway inflammation, suggesting a possible role of skin-derived TSLP in promoting the progression from AD to asthma. However, both studies used adjuvant Alum to sensitize the mice with high level of circulating TSLP, conditions not seen in AD patients. Whether and how TSLP is involved in the sequential progression from AD (peaking at 1-2 years old) to asthma (peaking around 5 years old) need further studies.

Inflammation can affect every aspect of tumor development and progression as well as the responses to therapies [128]. Recent studies demonstrating that progression of breast cancer [131, 133] and pancreatic cancer [132] are associated with TSLP-dependent induction of Th2-type inflammation will surely stimulate interest among oncology researchers. Neutralization of human TSLP inhibited breast cancer growth in a xenograft model [131], and inactivation of mouse TSLP in tumors alone or disabling its signaling by knocking out TSLPR was sufficient to diminish both breast cancer progression and metastasis [133]. In addition, tumor-derived TSLP may also help lung cancer cells escape host immune surveillance by inducing Treg differentiation in and migration to tumor tissues [135]. These results suggest that targeting TSLP could be an attractive new therapeutic treatment against various cancers.

Increased amounts of TSLP were found in synovial fluid specimens derived from patients with rheumatoid arthritis (RA) when compared with those from patients with osteoarthritis [141]. Anti-TSLP neutralizing antibody ameliorated a TNF-α-dependent experimental arthritis induced by anti-type II collagen antibody in mice. Administration of TSLP significantly exacerbated the severity of collagen-induced arthritis and the joint damage that was associated with increased T cell activation. In contrast, TSLPR-deficient mice had less severe proteoglycan-induced arthritis than did wild-type mice [142]. Although *Helicobacter pylori* induced chronic atrophic gastritis is characterized by marked infiltration of Th1 cells, *H. pylori*-infected epithelial cells produced TSLP, which in turn activated DCs to prime Th2 cells [17]. Considering pro-inflammatory and inflammatory cytokines induce TSLP in various tissues [9, 28, 132], it won’t be surprising to find that TSLP has a more generalized function in inflammatory diseases in addition to Th2 mediated diseases.

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