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REVIEW ARTICLE

Review Series: TSLP

Mouse Models of Allergic Diseases: TSLP and Its Functional Roles

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ABSTRACT

The cytokine TSLP was originally identified in a murine thymic stromal cell line as a lymphoid growth factor. After the discovery of TSLP, extensive molecular genetic analyses and gene targeting experiments have demonstrated that TSLP plays an essential role in allergic diseases. In this review, we discuss the current status of TSLP and its functional role in allergic diseases particularly by focusing on effects of TSLP on haematopoietic cells in mouse models. It is our conclusion that a number of research areas, i.e., a new source of TSLP, effects of TSLP on non-haematopoietic and haematopoietic cells, synergistic interactions of cytokines including IL-25 and IL-33 and a regulation of TSLP expression and its function, are critically needed to understand the whole picture of TSLP involvement in allergic diseases. The mouse models will thus contribute further to our understanding of TSLP involvement in allergic diseases and development of therapeutic measures for human allergic diseases.

KEY WORDS

allergic inflammation, allergic rhinitis, asthma, atopic dermatitis, atopic march, mouse models, Th2 cytokines, TSLP

INTRODUCTION

Epithelial cells in skin, lung, nasal cavity and gut are responsible for the first line of defense against foreign antigens and microbes. Epithelial cell-derived cytokines and chemokines that are secreted in response to infection and antigen exposure act on resident and circulating leukocytes and lead to subsequent immune response. In allergic diseases, i.e., atopic dermatitis (AD), asthma, allergic rhinitis and food allergy, epithelial cells produce cytokines including thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. Allergic diseases share a common pathogenesis involving overproduction of T helper 2 (Th2)-cytokines (IL-4, IL-13 and IL-5) and elevated IgE. Epithelial-derived allergic-inflammatory cytokines, i.e., TSLP, IL-25 and IL-33, are strongly associated with Th2 cytokines: TSLP indirectly and directly induces differentiation of Th2 cells[1-3]; IL-25 also primes $CD4^+$ T cells into Th2 cells and acts on epithelial cells to express TSLP[4,5]; IL-33 enhances Th2 cytokine secretions in Th2-polarized cells.[6] Mainly produced by Th2 cells, pro-allergic Th2 cytokines induce B cells to produce IgE. Since mechanisms for immune cascades involving known factors in allergic diseases have not been fully understood, our present review will focus on TSLP and describe how TSLP plays a role in allergic diseases of mouse models through immune cascades.

INITIAL CHARACTERIZATION OF TSLP

The cytokine TSLP was originally identified in 1994 as a biologically active factor from the conditioned medium of a murine thymic stromal cell line Z210R.1.[7] Since the conditioned medium used for the discovery of TSLP supported the proliferation of pre-B cell line NAG8/7, it was suspected that TSLP might be one of factors for B cell development. It was then reported that severe B and T cell lymphopenia occurred in the periphery of IL-7 receptor (IL-7Rα and

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common-γ)- and IL-7-deficient mice.[8-11] In this lymphopenia, B cell development was blocked at a transition from pre-pro-B to pro-B cells in bone marrow of IL-7R-deficient mice.[8-10] In IL-7-deficient mice, on the other hand, a transition from pro-B to pre-B cells was blocked.[11] Although the absolute cell number had decreased in IL-7-deficient mice, mature B cells still existed in the periphery, indicating that an unknown cytokine could drive B cell differentiation.[8-11]

One of the candidates for this unknown cytokine is actually TSLP. Since TSLP uses IL-7Rα subunit, sharing with the IL-7R complex, it was thought that the biological characteristics of TSLP, i.e., lymphopoietic activity, overlapped with IL-7. When precursors from either fetal liver or adult bone marrow were cultured in the presence of either TSLP or IL-7, TSLP was shown to promote the development of $B220^+/IgM^+$ immature B cells whereas IL-7 facilitated the development of $B220^+/IgM^-$ pre-B cells.[7,12] Taken together, since development of B cell precursors was blocked at different stages in IL-7Rα-deficient and in IL-7-deficient mice, it was strongly suggested that TSLP might utilize a unique TSLP-receptor (TSLPR) in combination with IL-7Rα chain.[12] Actual characterization of TSLP and its receptor began when molecular genetic analyses and gene targeting experiments started in mice.

TSLP AS A POTENTIAL KEY PLAYER FOR ALLERGIC DISEASES

cDNA clones expressing TSLP[13] and its receptor[14] were obtained by using expression cloning techniques whereas human sequences of TSLP and its receptor were identified *in silico* methods.[15] Since then, a variety of approaches have been made to determine TSLP function. *In vitro* studies using a recombinant TSLP protein showed enhanced IL-1-induced proliferation of $CD4^-CD8^-$ thymocytes, whereas TSLP alone had minimal activity.[13] Furthermore, TSLP was shown to promote B cell development in bone marrow cultures.[12]

Several TSLP-expressing transgenic mouse lines have been generated. Mice expressing TSLP under the control of the *lck*-proximal promoter preferentially acting early in thymocyte development and subsequently in T cells were generated. These mice displayed abnormal thymic structure and contracted a systemic inflammatory disease involving the kidney, liver, spleen, lungs, skin and mixed cryoglobulin formation.[16] TSLP transgenic (Tg) mice under the control of ubiquitous β-actin composite promoter developed unbalanced lymphopoiesis and myelopoiesis, and 40 to 80% of the mice died prematurely.[17] In these Tg mice, the dramatic increase in serum IL-5 levels was observed, suggesting that TSLP involvement might be in pro-allergic immune responses.[17] Interestingly, Soumelis *et al*. showed that, in humans, TSLP-activated dendritic cells (DCs) primed naïve $CD4^+$ T cells into Th2 cells that secreted IL-4, IL-13 and IL-5.[18] In addition, TSLP expression was significantly elevated in the epidermis of lesional skin from both acute and chronic AD patients.[18] These results all suggested that TSLP could be a potential key player for allergic diseases in mice and humans.

Since Soumelis *et al*. made their report, a series of studies using mouse models has focused on effects of TSLP in allergic diseases. A crucial role of TSLP in the development of AD and allergic asthma became also evident when Tg mouse lines were used. Since TSLP is expressed primarily by epithelial cells,[18] a number of Tg mouse lines have been generated to determine effects of TSLP in allergic diseases: inducible keratin 5 (K5)-[19] and constitutive K14-[20,21] TSLP Tg mice for AD where TSLP is specifically expressed in the epidermis; constitutive surfactant protein C (SPC)-TSLP Tg mice[22] for allergic airway inflammation where TSLP is specifically expressed in the lung epithelial cells. The studies using these Tg mice showed that the expression of TSLP both in the skin and in the lung resulted in development of a spontaneous inflammation with the hallmark feature of AD and allergic airway inflammation, respectively. Therefore, TSLP mouse models to trace allergic symptoms have now become the major research tool for allergic diseases, despite the poor homology (43%) of amino acids of TSLP between mice and humans.[15]

INDUCTION OF TSLP BY EXOGENOUS FACTORS

To investigate the involvement of TSLP in non-transgenic allergic disease models, three types of models have been used: (1) antigen-driven models using ovalbumin (OVA), (2) a protease model and (3) a model of Th2-type contact hypersensitivity. In the OVA-induced airway inflammation model, increased levels of TSLP were observed, whereas TSLPR-deficient mice displayed reduced airway inflammation and goblet cell hyperplasia.[22,23] Epicutaneous immunization of mice with OVA induced allergic skin inflammation including skin infiltration of eosinophils, increased levels of Th2 cytokines in the skin and OVA-specific serum IgE, all of which significantly decreased in TSLPR-deficient mice.[24] OVA-induced allergic diarrhea accompanied by Th2 cytokine production in gastrointestinal tract was also TSLP-TSLPR signal-dependent.[25] Finally, in OVA-induced allergic rhinitis, treatment with a neutralizing anti-TSLP antibody decreased its symptoms[26] (Fig. 1).

A recent study has reported that mechanical injury in the skin induced temporary TSLP expression.[27] In the presence of OVA antigen, DCs isolated from the skin of wild-type mice after mechanical injury elicited increase in IL-4 and IL-13 productions in $CD4^+$ T cells with OVA-specific T cell receptor, whereas DCs from the injured skin of TSLPR-deficient mice or from the skin of un-injured mice induced the production of

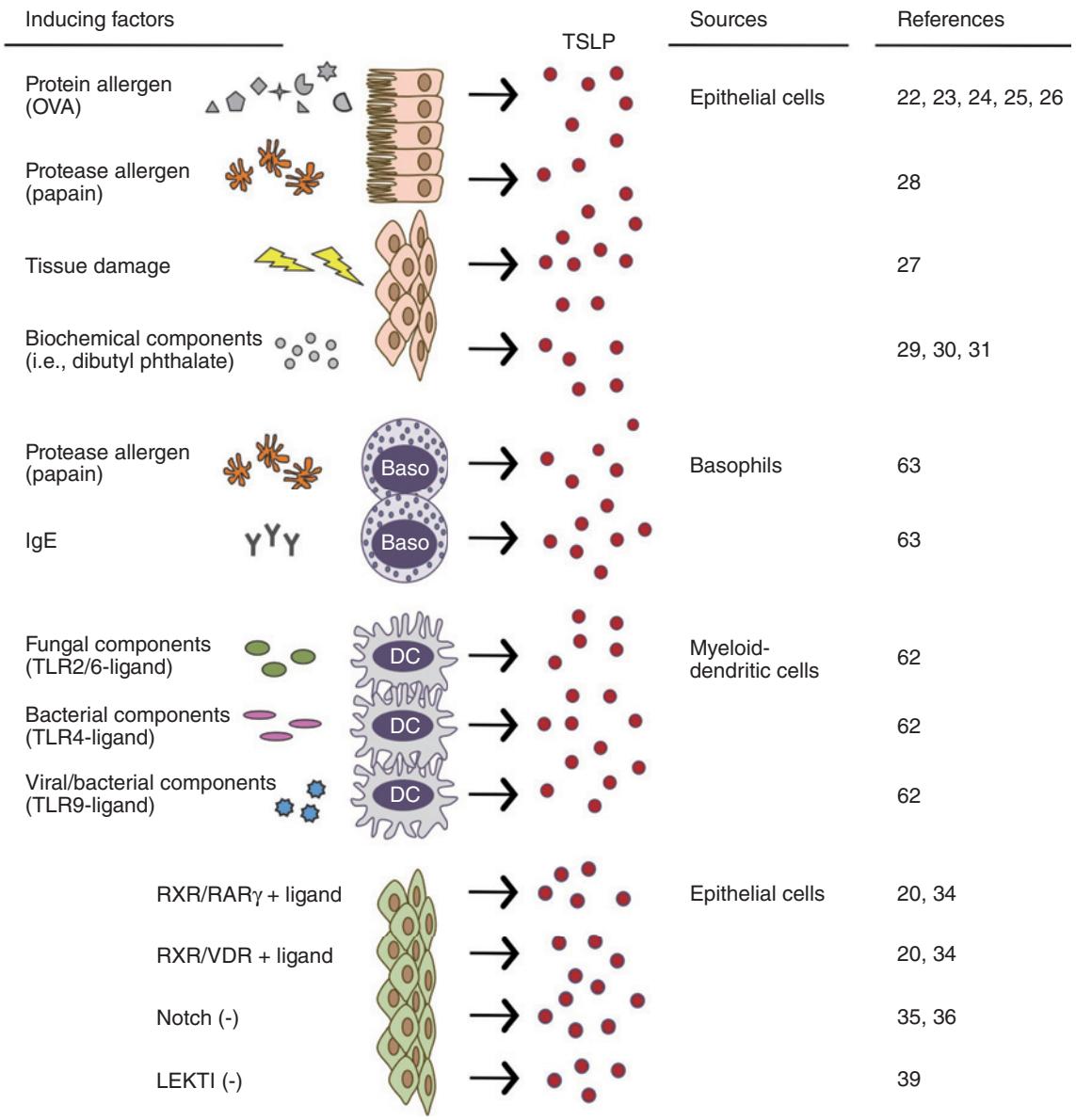


Fig. 1 Inducing factors and sources of TSLP in mice. Epithelial cells (airway epithelial cells, epidermal keratinocytes, intestinal epithelial cells and nasal epithelial cells), basophils and DCs are all capable of producing TSLP in the presence of exogenous and endogenous factors in mice. Note that epidermal keratinocyte-specific RXRαβ-deficient mice express TSLP (reference 20).

both the cytokines at a relatively smaller amount.[27] The study suggests that a protein antigen such as OVA raises TSLP expression and that an increased level of TSLP even temporarily in the skin by mechanical injury enhances antigen-derived Th2 responses by skin DCs (Fig. 1).

In addition to OVA, proteases also act as allergens. For instance, a cysteine protease papain was shown to induce the expression of *Tslp* in the injected site of the skin in wild-type mice (Fig. 1). This expression of *Tslp* was dependent on reactive oxygen species (ROS), toll-like receptor (TLR) 4 and the adaptor protein TIR-domain-containing adaptor-inducing interferon-β (TRIF).[28]

TSLP was induced in an experimental model of Th2-type contact hypersensitivity, using FITC as an allergen (a model for human Th2-type contact hypersensitivity).[29-31] A component of the solvent used in this model, dibutyl phthalate, was shown to induce TSLP expression[29-31] (Fig. 1). In the absence of TSLP responses, there was a profound decrease in type-2 immune responses in the skin and in antigen-bearing DCs in the draining lymph node following FITC treatment, and the DCs that did migrate displayed a de-

creased capacity for promoting $CD4^+$ T cell proliferation.[29] All of the reports demonstrate that the factors including OVA, proteases and dibutyl phthalate act as inducing agents of TSLP and that TSLP is necessary and sufficient for allergic inflammation in mice.

INDUCTION OF TSLP BY ENDOGENOUS FACTORS

It has become also clear that mutations affecting skin function can alter the expression of *Tslp* and lead to inflammation. The keratinocyte-specific inducible ablation of retinoid X receptors (RXRα and RXRβ) in adult mice resulted in TSLP-dependent spontaneous dermatitis with reddening, swelling and scaling[20] (Fig. 1). In the inflamed skin of RXRαβ-deficient mice, Th2-type cytokine expression and leukocyte infiltration consisting of $CD4^+$ T cells, DCs, eosinophils and mast cells were observed.[20] RXRs belong to the nuclear receptor (NR) superfamily and function by forming either a homodimer or heterodimers with partners such as vitamin D receptor (VDR), retinoic acid receptor (RAR) family and PPARβ.[32] Since heterodimers of RXR/NR regulate transcriptions of target genes,[33] the release of RXR/NR mediated-transcriptional repression could explain an elevated expression of TSLP in epidermal keratinocyte-specific RXRαβ-deficient mice. In their followup study, Li and colleagues identified the NR partners of RXRα and -β for the induction of TSLP. Among the agonists of RXR partners, topical application of the agonistic ligand for vitamin D3 and RARγ-selective ligand on ear skin induced TSLP expression in epidermal keratinocytes[34] (Fig. 1). The results suggested that the ligation of RXR/VDR and RXR/RARγ with those ligands induced the expression of *Tslp*.

Epidermal-specific mutations in the Notch pathway (Notch1, Notch2, or RBP-j, DNA binding partner of Notch) resulted in a severe form of AD and B-lymphoproliferative and myeloproliferative disorder via TSLP-TSLPR signaling[35,36] (Fig. 1). Notch signaling contributes to terminal differentiation of keratinocytes in skin.[37] The skin of AD patients showed markedly reduced Notch expression in epidermis, implying a possible link between a downregulation of the Notch signal and development of AD through upregulation of TSLP.[36]

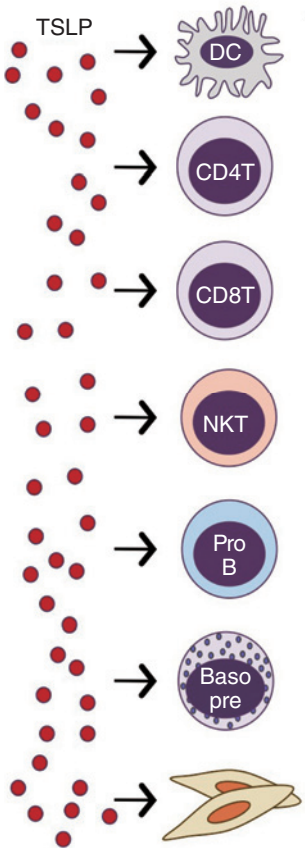
The involvement of nuclear factor κB (NFκB) signaling in TSLP expression by mouse intestinal epithelial cells[38] implicates a possibility that NFκB may be involved in TSLP expression in allergic inflammations. Mice lacking the multi-domain serine protease inhibitor *Spink5* expressed TSLP in the epidermis along with proinflammatory and Th2-polarizing molecules. *Spink5*, mutated in individuals as human Netherton syndrome, dysregulates epidermal proteases such as Kallikrein 5 (KLK5). In mice, a lack of *Spink5* product (lymphoepithelial Kazal-type-related inhibitor (LEKTI)) resulted in expressions of protease-activated receptor 2 (PAR-2) and TSLP and mRNA of *F2rl1*, *Tslp* and *Tnf* (Fig. 1).[39] In addition, protease activation of PAR-2 inducing expression of *TSLP* has been observed in a number of settings using the human bronchial epithelial cell line BEAS-2B.[40] Since TNFα induces TSLP expression in intestinal epithelial cells and because NFκB mediated the TSLP expression by TNFα,[38] the induction of TSLP expression by TNFα and/or PAR2 may possibly be mediated by NFκB signaling in *Spink5* deficient mice. In fact, human *TSLP* expression in keratinocytes was downregulated in the presence of an inhibitor for NFκB pathway.[39] Taken together, a wide variety of endogenous factors were found to induce TSLP expression and subsequent Th2-type inflammation. Our challenge will be to elucidate signaling pathways involved in each of the endogenous factor in allergic diseases.

EFFECTS OF TSLP ON LEUCOCYTES

TSLP signals cells via a TSLPR-IL-7Rα heterodimer.[14,41] TSLP-TSLPR signaling activates STAT5 in mice but STAT1 and 5 and possibly STAT3, 4 and 6 in humans.[3,42,43] TSLP-mediated phosphorylation of STAT5 was induced via JAK1 and JAK2 in mouse $CD4^+$ T cells whereas IL-7 signals through JAK1 and JAK3 to activate STAT5.[43] Several bone marrow-derived cells, i.e., DCs, $CD4^+$ T cells, $CD8^+$ T cells, NKT cells, early B cell precursors and basophil progenitors, are capable of responding to TSLP.

As studied extensively in humans, DCs are likely to be the primary target of TSLP in mice. When they were exposed to TSLP, mouse and human DCs increased the cell surface expressions of CD40, CD80, CD86 and MHC class II[18,22,23] (Fig. 2). These TSLP-activated DCs enhanced antigen-mediated proliferation of $CD4^+$ T cells.[23] Furthermore, OX40L was expressed in OVA antigen-captured DCs in mediastinal lymph node of the mice administered with OVA plus TSLP, but not in OVA-uncaptured DCs.[44] In addition, *in vivo* blockade of OX40L with a specific antibody inhibited TSLP-driven Th2-type inflammation.[44] Since OX40L is expressed on professional antigen-presenting cells including DCs and because activated $CD4^+$ and $CD8^+$ T cells and most memory T cells display the receptor, OX40,[45] it is suggested that in response to TSLP, DCs may become activated and initiate T cell-mediated Th2-type inflammation via OX40L as reported in humans.[3]

$CD4^+$ and $CD8^+$ T cells are also capable of responding to TSLP (Fig. 2). Resting mouse $CD4^+$ and $CD8^+$ T cells expressed TSLPR and IL-7Rα at similar levels, whereas human unactivated $CD4^+$ and $CD8^+$ T cells did not express TSLPR.[46] During Th2 differentiation in mice, the expression of *Tslpr* and *Il7ra* subunits was once downregulated after TCR-stimulation and then was gradually upregulated (M.O.-M. unpublished data) at a higher level in differentiated effector



Subsets that express TSLPR	Events	References
Dendritic cells	MHC II⇧, CD40⇧, CD80⇧, CD86⇧, CCL17⇧	22, 23
$CD4^+$ T cells	Proliferation⇧, Th2 differentiation (IL-4⇧, IL-5⇧, IL-13⇧)	24, 47, 48, 49
$CD8^+$ T cells	Survival⇧	46
NKT cells	IL-13 production⇧	51
Pro-B cells	Expansion⇧	52
Basophil precursors	Expansion of mature basophils IL33R⇧, IL-4⇧, IL-6⇧, Cxcl2⇧, CCL3⇧, CCL4, CCL12⇧	53
Fibrocytes	Collagen production⇧	64

Fig. 2 Target cell populations of TSLP in mice. Dendritic cells, activated $CD4^+$ T cells, differentiated $CD4^+$ Th2 cells, activated $CD8^+$ T cells, activated NKT cells, pro-B cells, basophil-precursors and fibrocytes are all responsive to TSLP.

Th2 cells than in other Th subsets.[47] TSLP directly drove highly purified naïve $CD4^+$ T cells into Th2 cytokine-secreting cells, an event that was not observed in TSLPR-deficient $CD4^+$ T cells.[48] This direct effect of TSLP on $CD4^+$ T cells agrees with two other reports: TSLP amplified Th2 cytokine secretion by engaging TSLPR on antigen-specific mouse $CD4^+$ T cells but not on DCs *in vitro*[24]; TSLP induced the phosphorylation of STAT5 in anti-CD3- plus anti-CD28-activated human $CD4^+$ T cells.[43] In addition, TSLP was capable of both enhancing proliferation of anti-CD3-activated $CD4^+$ T cells and differentiated effector Th2 cells[47,49] and promoting the survival of both $CD4^+$ and $CD8^+$ T cells.[46,49] These studies suggest that TSLP preferentially expands Th2-type $CD4^+$ T cells and contributes to both $CD4^+$ and $CD8^+$ T cell homeostasis.

In development of allergic asthma, activation of NKT cells is critically involved.[50] NKT cells expressed both TSLPR and IL-7Rα, and anti-CD3-activated NKT cells produced IL-13 in the presence of TSLP (Fig. 2). In SPC-TSLP Tg mice with elevated levels of lung-specific TSLP, a lack of NKT cells resulted in reduced airway hyperresponsiveness after an antigen challenge.[51] These results suggest that IL-13 produced by TSLP-stimulated NKT cells could aggravate asthmatic symptoms.

As described above, TSLP was initially described to be a B cell growth and differentiation factor. Subsequent *in vivo* studies have supported these results. K5-TSLP Tg mice expressing an inducible TSLP transgene in the epidermis displayed highly circulating levels of TSLP when they were treated with doxycycline.[52] These mice showed (1) an influx of immature B cells from bone marrow into the periphery, (2) a population expansion of follicular mature B cells and peritoneal B-1b cells and (3) a loss of marginal zone B cells. Among developmental subsets of B cells, pre-pro-B cells and pro-B cells expressed both TSLPR and IL-7Rα. The pro-B cells were expanded in the presence of TSLP (Fig. 2). The analysis of K5-TSLP Tg mice as well as *in vitro* studies identified late pro-B cells as a key TSLP-responsive subset and the effect of TSLP led to developmental abnormalities of B cells.[52] Although one study showed that human B cells expressed neither TSLPR nor IL-7Rα,[15] TSLP

promoted the differentiation of $CD19^+VpreB^+$ pre-B cells that were derived from $CD34^+$ human cord blood progenitors.[52]

Recently, TSLP was discovered to promote basophil haematopoiesis from bone marrow resident precursors. In fact, SPC-TSLP Tg mice have elevated basophil numbers and TSLP was shown to promote basophils differentiation from precursors in the bone marrow in the absence of IL-3-IL-3R signaling.[53] In addition, basophils contributed to Th2 responses by supplying Th2 cytokines and presenting antigens to $CD4^+$ T cells.[54-56] Moreover, TSLP-elicited basophils expressed IL-33R at relatively higher level than IL-3-elicited basophils[53] (Fig. 2). Once basophils were expanded in a TSLP-dominant allergic environment, they could play a key role in the development of allergic symptoms by producing a Th2 cytokine IL-4 and increasing a susceptibility to IL-33 (another allergy-associated cytokine). Since there was only one report on effects of TSLP on basophil haematopoiesis, more studies will be needed to examine interactions of basophils with TSLP and IL-33.

THE ATOPIC MARCH AND TSLP

Atopic diseases including AD, asthma, and allergic rhinitis share common features such as overproduction of Th2-cytokines leading to eosinophilia and IgE-mediated responses to allergens. Since children with AD tend to develop allergic asthma later in life and because severity of eczema of AD is associated with sensitivity to asthma and allergic rhinitis, AD is the major risk factor for developing other atopic diseases.[57,58] Recently, a role of TSLP as a potential factor linking to the atopic march has been investigated. As observed in mice treated with a vitamin D3 analog or in the skin of K14-TSLP Tg mice, TSLP that was highly expressed in epidermis aggravated the allergic responses in the lung that were induced by OVA.[59,60] These mice displayed a very high level of circulating TSLP. Similar results were also obtained in K5-TSLP Tg mice (S.F.Z. and H. Han, manuscript in preparation). The above results suggest that elevated circulating TSLP plays a confounding role in these studies. This conclusion is supported in part by a recent study of Zhu and colleagues.[61] In this report, mice with epidermal-specific expression of IL-13 developed AD and showed enhanced airway inflammation following allergen challenge. Interestingly, these mice also showed elevated TSLP expression in the skin, but circulating TSLP was barely detectable. This lung inflammation was reduced in TSLPR-deficient environment,[61] suggesting that IL-13-mediated local expression of TSLP in the skin may be critical to sensitize the lung to allergen challenge. Although all these reports clearly demonstrate an important role of TSLP in the atopic march, a role of circulating TSLP in different settings of the atopic march remains to be investigated.

CONCLUSIONS

The present review of TSLP in mouse models provides the current status of TSLP and its functional role in allergic diseases, particularly by focusing on the effects of TSLP on haematopoietic cells. As clinical trials using TSLP neutralizing antibodies are currently underway, the mouse models described in this review will be an invaluable complement to the human clinical studies. However, several areas of research on TSLP will be needed to have a better understanding of the underlying mechanisms for development of allergic diseases. A new source of TSLP should be explored, since it was reported that human monocyte-derived and mouse bone marrow-derived DCs actually produced TSLP in the presence of a ligand for TLR2/6, -4 or -9[62] and that mouse basophils expressed *Tslp* in response to active papain or IgE crosslinking[63] (Fig. 1). Studies of effects of TSLP on non-haematopoietic cells such as fibrocytes[64] (Fig. 2), synergistic interactions of TSLP with epithelial-derived cytokines IL-25 and IL-33 and a regulation of TSLP expression and its function will all be critically needed to uncover how TSLP involves in a particular allergic disease and in the atopic march. All the efforts will facilitate further development of therapeutic measures for human allergic diseases.

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