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Review

Thymic stromal lymphopoietin and atopic diseases

La cytokine Thymic Stromal LymphoPoietin (TSLP) et les maladies atopiques

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Abstract

Studies from the last ten years have seen great progress in recognizing the role of cytokine thymic stromal lymphopoietin (TSLP) in pathogenesis of atopic diseases, particularly atopic dermatitis (AD) and asthma. We provide here a review of the findings from four aspects: (1) TSLP: expression triggers and cellular sources; (2) TSLP receptor: cellular sources; (3) TSLP-TSLP receptor signaling; and (4) TSLP in atopic diseases: from mouse models to cellular and molecular mechanisms.

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Keywords: Cytokine; Thymic stromal lymphopoietin (TSLP); TSLP receptor; Atopic diseases; Atopic dermatitis; Asthma

Résumé

Les études de ces dix dernières années ont vu de grands progrès dans la reconnaissance du rôle de la cytokine Thymic Stromal LymphoPoietin (TSLP) dans la pathogenèse des maladies atopiques, et en particulier la dermatite atopique (DA) et l'asthme. Nous fournissons ici un compte rendu des résultats de recherches à partir de quatre aspects : (1) TSLP : expression et sources cellulaires ; (2) récepteur de la TSLP : sources cellulaires ; (3) signalisation du récepteur de la TSLP ; et (4) TSLP dans les maladies atopiques : des modèles murins aux mécanismes cellulaires et moléculaires.

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Mots clés : Cytokine ; Thymic stromal lymphopoietin (TSLP) ; Récepteur de la TSLP ; Maladies atopiques ; La dermatite atopique ; L'asthme

1. Introduction

Atopic diseases, including AD (known also as eczema) [1], asthma [2], allergic rhinitis (AR) and food allergy, are closely related inflammatory diseases involving different body sites i.e. skin, airways and digestive tract, with common features including the production of specific IgE to allergens (so called “atopy”), and Th2 inflammation. Moreover, an individual often experiences the progression from AD to asthma and/or AR, which is clinically called the “atopic march” [3]. The

prevalence of these diseases has markedly increased over the last decades and represents an important health and financial burden.

In the last ten years, the cytokine TSLP expressed mainly by epithelial cells has been recognized as a key player in the pathogenesis of various human diseases, including allergy, infection, autoimmunity and cancer. Among these, the initial and most extensive studies, including ours, are in the context of atopic disorders. We provide here a review on the great number of data on the expression and cellular sources of TSLP and its receptor, the TSLP-TSLP receptor signaling, and what we have learned from mouse models to cellular and molecular mechanisms, concerning the role of TSLP in the pathogenesis of atopic diseases.

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2. TSLP: expression triggers and cellular sources

TSLP is a type I cytokine belonging to IL-2 family. Initially, mouse TSLP was discovered as a cytokine produced by thymic stromal cell line that supported B cell development [4–6]. A human homolog of TSLP was subsequently identified and characterized [7,8]. Although murine and human TSLP share a poor amino acid identity (43%), their expression as well as function has been shown to present significant similarities.

TSLP mRNA expression was initially reported in a panel of human cell lines and primary cells including epidermal keratinocytes (KCs), epithelial cells (ECs), smooth muscle cells, lung fibroblasts and mast cells, but not in most hematopoietic cell types [9]. As detailed below, studies have suggested that TSLP expression is induced by a variety of environmental stimuli, and it is also linked with a number of gene mutations (Table 1).

2.1. Allergens

Protease allergens like papain and extracts of the fungus *Alternaria* induced TSLP expression in human bronchial EC line [10]. In addition, multiple protease allergens (papain, spargillus protease and Der p1) triggered the TSLP expression in mouse lung ECs (MLE12) and primary mouse lung ECs, as well as in mouse embryonic fibroblast cells [11]. Upon *intradermal* papain injection, increased TSLP expression was reported in mouse epidermis [12] and in basophils [13]. In addition, *intratracheal* instillation of aeroallergen HDM (house dust dities) induced TSLP expression in lung ECs as well as in dendritic cells (DCs) [14]. Moreover, administration of ragweed pollen extract to mouse ocular surfaces induced TSLP production in corneal and conjunctival epithelia [15,16].

2.2. Viruses

Rhinovirus RV16 promoted TSLP expression in human airway ECs [17,18]. Respiratory syncytial virus (RSV) induced TSLP production in primary rat airway ECs [19]. Primary human KCs produced TSLP in response to the infection of vesicular stomatitis virus (VSV) [20]. Moreover, human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) induced TSLP expression in human cervical EC lines and in primate vaginal tissues, respectively [21].

2.3. Microbes

Live and UV-killed commensal bacteria induced the production of TSLP in human colon cancer cell line Caco-2 [22]. TSLP was detected in follicular gastritis patients with *Helicobacter pylori* (*H. pylori*) infection, and TSLP production was reported in human gastric EC line upon the direct contact with *H. pylori* [23]. Recently, TSLP gene expression was reported to be activated by gut microbiota containing a variety of commensal bacteria [24,25]. Moreover, *Staphylococcus aureus* (*S. aureus*) and *Malassezia yeasts*, two exacerbating

factors for AD, stimulated TSLP production in primary human KCs [26,27].

2.4. Parasites

Mice infected with intestinal-dwelling parasite *Trichuris muris* [28,29] or *Trichinella spiralis* [30,31] exhibited an upregulated TSLP expression in the intestine. In addition, excretory-secretory proteins from *T. spiralis* induced TSLP production in mouse colon EC line [30].

2.5. Ligands of pattern recognition receptors

Toll-like receptor (TLR) ligands, such as TLR3 ligand (synthetic double-stranded RNA) and TLR2 ligand (peptidoglycan; PGN) [32], have been shown to promote TSLP expression in primary human airway ECs. Other reports showed that TSLP expression was increased in normal human bronchial epithelial (NHBE) cells upon the treatment of agonists for TLR2, TLR8 and TLR9 [33], or TLR3 [18]. TSLP production in nasal ECs from healthy mucosa was shown to be induced by a wide range of TLR agonists including poly (I:C) (TLR3 agonist), flagellin (FLA; TLR5 ligand), R848 (TLR7/8 agonist) and PGN [34]. Increased amount of TSLP was found in mouse airways upon FLA instillation, and moreover, FLA-treated primary mouse airway ECs produced higher amount of TSLP [35]. Besides, accumulating data showed that various TLR ligands induced TSLP expression in KCs, corneal ECs, oral ECs, colonic ECs, as well as non-EC cells such as synovial fibroblasts and DCs (see Table 1).

Intracellular nucleotide-binding oligomerization domain (Nod)-like receptors (NLRs) represent another class of pattern recognition receptors. In mice, *intranasal* (*i.n.*) treatment of the Nod2 ligand was shown to induce TSLP expression in the lung [36].

2.6. Ligands of nuclear receptors

Previous studies from our lab reported that whereas TSLP expression was trans-repressed by un-liganded nuclear receptors, i.e. retinoid X receptor (RXR)/vitamin D receptor (VDR) and RXR/retinoic acid receptor (RAR) in mouse skin KCs [37], it was activated by physiologically active ligand for VDR (1, 25-dihydroxyvitamin D3) or its low-calcemic analog MC903 (calcipotriol), or by all-trans retinoic acid (at-RA) and RAR γ -selective agonist (BMS961) [38]. Glucocorticoids (GCs), ligands of GR (GC receptor, which also belongs to nuclear receptor superfamily) were shown to inhibit the expression of TSLP [18,39–41]. Notably, a negative GRE (glucocorticoid-responsive element) was identified in the TSLP promoter region, which mediated the GC-induced direct transrepression [41].

2.7. Chemicals

Topical treatment with chemical compounds, such as dibutyl phthalate (DBP; a commonly used plasticizer), toluene, xylene

Table 1

TSLP expression triggered by environmental stimuli and genetic factors.

The trigger for TSLP expression	Cell type	References
Allergens		
Proteases: trypsin, papain and <i>Alternaria</i> extract	Human bronchial epithelial cell line BEAS-2B	[10]
Proteases: papain, <i>Aspergillus</i> protease and <i>Der p1</i>	Mouse lung epithelial cell line MLE12 and primary mouse lung epithelial cells	[11]
Papain	Mouse epidermis	[12]
Papain	Mouse basophils	[13]
HDM intratracheally administered	Mouse lung epithelial cells and DCs	[14]
<i>Ambrosia artemisiifolia</i> short ragweed pollen	Human corneal epithelial cells	[15]
<i>Ambrosia artemisiifolia</i> short ragweed pollen	Mouse corneal and conjunctival epithelia	[15,16]
Viruses		
Rhinovirus 16, dsRNA and dsRNA-LyoVec	Primary bronchial epithelial cells from patients with chronic obstructive pulmonary disease	[17]
Rhinovirus 16 and dsRNA	Normal human bronchial epithelial cells (NHBE)	[18]
Respiratory syncytial virus	Primary rat airway epithelial cells	[19]
Vesicular stomatitis virus and Poly (I:C)	Human primary keratinocytes	[20]
HIV-1 _{IIIB} (X4 strain), HIV-1 _{YU2} (R5 strain), HIV-1 isolate 93ZR001.3, HIV-1 _{ADA} and HIV-1 _{IMN}	Adult normal human epidermal keratinocytes	[21]
SIVmac251 intravaginally inoculated	Vaginal tissues from rhesus macaques	[21]
Microbes		
Live and UV-killed bacterias from <i>Lactobacilli</i> , <i>Bifidobacteria</i> , <i>Escherichia coli</i> and <i>Klebsiella</i> strains	Human epithelial colorectal cell line Caco-2	[22]
<i>Helicobacter pylori</i> strain TN2GF4	Human gastric epithelial cell lines MKN28, MKN45 and MKN74	[23]
Commensal bacteria	Primary mouse colon	[24,25]
Heat-killed <i>Staphylococcus aureus</i> , membrabous fraction of <i>S. aureus</i>	Primary human keratinocytes	[27]
Live or n-octyl- β -d-glucoside (OG)-extracted fraction from <i>Malassezia globosa</i> and <i>Malassezia restricta</i>	Primary normal human epidermal keratinocytes	[26]
Parasites		
<i>Trichuris muris</i> infection	Mouse intestine and caecal tissue	[28,29]
<i>Trichenella spiralis</i> infection	Mouse small intestine	[31]
Excretory-secretory protein from <i>Trichinella spiralis</i>	Mouse colon epithelial cell line CT-26	[30]
Pattern recognition receptor ligands		
Poly (I:C), flagellin, R848 and PGN	Nasal polyp epithelial cells	[18,34]
Lipoteichoic acid, poly (CpG), CpG-B and poly (I:C)	Nasal epithelial cells from healthy individuals, Normal human bronchial epithelial cells (NHBE)	[33,127]
Poly (I:C), flagellin, R848 and PGN	Respiratory airway epithelial cell line H292	[34]
Flagellin	BALF and primary mouse airway epithelial cells	[35]
Poly (I:C)	Primary human keratinocytes	[128]
Synthetic diacylated lipopeptide FSL-1	Primary human keratinocytes	[27]
Flagellin	Primary human keratinocytes	[129]
Pam ₃ Cys, HKLM, LPS, Poly (I:C), flagellin, FSL-1 and CpG ODN	Human keratinocyte cell line HaCaT	[130]
Poly (I:C), FSL-1 and flagellin	Primary human keratinocytes	[131]
Poly (I:C), flagellin, and FSL-1	Primary human corneal epithelial cells	[132]
Poly (I:C)	Oral epithelial cells	[133]
Flagellin	Human colon cancer cell line Caco-2	[134]
Poly (I:C) and LPS	Primary human synovial fibroblasts	[40]
LPS or zymosan	Human peripheral blood monocytes and monocyte-derived DCs	[14]
Zymosan, LPS, CpG and flagellin	GM-CSF derived mouse bone marrow DCs or splenic DCs	[14]
Nod2 ligands	Mouse lungs	[36]
Nuclear receptor ligands		
Active vitamin D3, MC903 (Calcipotriol), retinoic acid and RAR γ agonists (BMS961)	Mouse skin	[38]
Fluticasone propionate	Normal human bronchial epithelial cells (NHBE)	[18]
Dexamethasone	Primary human synovial fibroblasts	[40]
Dexamethasone	Primary human keratinocytes	[39]
Fluocinolone acetoneide	Mouse skin	[41]
Chemicals		
Toluene, xylene, trimethylbenzene and DBP	Mouse skin	[42–44]
12-O-tetradecanoylphorbol 13-acetate (TPA)	Mouse ear skin	[41,45]

Table 1 (Continued)

The trigger for TSLP expression	Cell type	References
Diesel exhaust particles	Primary human bronchial epithelial cells	[46,47]
Cigarette smoke extract	Primary human airway smooth muscle cells	[49]
Cigarette smoke extract	Mouse lungs	[48]
Skin barrier dysfunction		
Tape stripping; detergent (sodium lauryl sulfate)	Human epidermis from healthy donors	[50]
Tape stripping	Mouse skin	[51]
Tape stripping	Mouse epidermal keratinocytes	[52]
Genetic mutations		
Selective ablation of nuclear receptor RXR α and β in adult keratinocytes	Mouse epidermis	[37]
Selective ablation of Notch1 and 2 in adult keratinocytes	Mouse epidermis	[53]
Selective ablation of RBP-j in keratinocytes	Mouse epidermis	[54]
<i>SPINK5</i> deficiency	Mouse epidermis and human epidermis from Netherton disease patients	[55]

and trimethylbenzene, were shown to promote TSLP expression in mouse ears [42–44]. Mouse skin TSLP production was also induced upon topical application of 12-O-tetradecanoyl-phorbol 13-acetate (TPA) [41,45].

In addition, diesel exhaust particles promoted TSLP expression in human bronchial ECs [46,47]. Cigarette smoke induced TSLP expression in mouse lung as well as in a human airway smooth muscle cell line [48,49].

2.8. Skin barrier dysfunction

Defective skin barrier function has been recognized as a critical factor in the initiation and exacerbation of AD as well as in the progression from AD to asthma. Impairment of stratum corneum in human skin by tape stripping or application of detergent (sodium lauryl sulfate), induced TSLP production in the epidermis [50]. Skin tape stripping has been also shown to promote TSLP production in epidermal KCs in mice [51,52].

2.9. Genetic mutations

Selective ablation of RXR α and β in epidermal KCs in mice led to an increase of TSLP production in the skin, which triggered an AD-like syndrome [37]. In addition, KC-specific deletion of Notch proteins (Notch 1 and 2) [53] or RBP-j (the DNA-binding partner of Notch) [54], which caused severe epidermal differentiation defects, also resulted in TSLP expression and Th2 skin inflammation. Recently, it has been shown that mutation of serine protease inhibitor Kazal-type 5 gene (*SPINK5*) in mice induced a high production of TSLP in skin [55]. In addition, mutations in human *SPINK5* gene have been identified to be responsible for the Netherton syndrome (NS), and overexpression of TSLP was detected in skin of NS patients [55].

3. TSLP receptor: cellular sources

TSLPR was initially identified as a cell-surface receptor that shares 24% identity with the common γ chain (γc), and binds TSLP with low affinity [56,57]. Further studies identified the

functional receptor of TSLP as a heterodimer of TSLPR and IL-7 receptor (IL-7R) α in both humans and mice [7,57]. As detailed below, the expression of TSLP receptor has been reported in a number of hematopoietic cell lineages, as well as in some non-hematopoietic cells (Table 2).

3.1. DC and monocytes

Initial analyses in a panel of cDNA libraries made from various tissues and cell types showed that human TSLPR and IL-7R α were principally coexpressed on monocytes and DCs and to a much lesser extent on various lymphoid cells [8]. Human monocyte-derived DCs cultured with supernatants from Caco-2 cell line or from primary ECs expressed both TSLPR and IL-7R α [58]. In addition, the expression of TSLPR and IL-7R α was detected in myeloid DCs in human tonsils [59]. In mice, TSLPR expression was as well found in DCs [60,61].

3.2. Activated T cells

Although TSLPR does not seem to be expressed by naïve resting T cells, it was reported that upon the activation by anti-CD3 plus anti-CD28, human CD4⁺ cells [62] or CD8⁺ cells [63] exhibited an increased expression of TSLPR. Recently, human TSLP receptor was shown to express on rare actively dividing Th2 cells in a “proallergic” milieu [64]. In mice, TSLPR expression was reported elevated on Th2, but not on Th1 nor Th17 cells [65].

3.3. B cell progenitors

During human B cell development, transcripts for the TSLPR were detected mainly in hematopoietic stem cells, multilineage-committed progenitor cells and pro-B cells from fetal liver and bone marrow. In contrast, pre-B cells and BCR⁺ B cells lacked its expression [66]. In mice, although TSLP was originally shown to influence B cell development and proliferation [5,67], the expression of TSLPR and IL-7R α was not fully explored.

Table 2
Cells expressing TSLP receptor and TSLP-mediated activity.

Cell types	Detection methods	TSLP-mediated activity	References
DCs and monocytes			
Human monocytes	IL-7R α and TSLPR by RT-PCR	Increased expression of chemokines CCL16, CCL17, CCL18, CCL19 and CCL22	[8]
Human purified immature CD11c ⁺ blood DCs	IL-7R α and TSLPR by RT-PCR and FACS	Slightly upregulation of HLA-DR and CD86 Strong upregulation of CD40 and CD80 Upregulation of OX40L expression Increased DC viability Increased allogenic naïve CD4 ⁺ T cell proliferation Induced inflammatory Th2 cells	[8,9,59,61,135]
Human monocyte-derived DCs exposed to supernatants of Caco-2 cell line	IL-7R α and TSLPR by RT-PCR	Th2 cell polarization and inhibition of Th1 cells	[58]
Mouse splenic DCs	TSLPR by RT-PCR	Moderate increase of MHCII, CD80 and CD86 expression Enhanced OVA-mediated proliferation of DO11.10 TCR transgenic CD4 ⁺ T cells Reduced levels of IFN γ in DO11.10 TCR transgenic CD4 ⁺ T cells Increased levels of OX40L expression	[60,103]
Mouse bone marrow-derived DCs	IL-7R α and TSLPR by FACS	Increased CCL17 expression Upregulation of MHCII, CD40, CD80 and CD86 expression	[102]
T cells			
Anti-CD3 and anti-CD28 activated human CD4 ⁺ T cells	IL-7R α and TSLPR by microarray and FACS	Weak CD4 ⁺ T cell proliferation Slight improvement of CD4 ⁺ T cell survival	[59]
Anti-CD3 and anti-CD28 activated human CD4 ⁺ T cells	TSLPR by RT-PCR, FACS and western blot	Increased proliferation of TCR-activated CD4 ⁺ T cells Induction of IL-2R α and CIS mRNA Increased IL-3 induced CD4 ⁺ T cell proliferation	[62]
Anti-CD3 and anti-CD28 activated human CD8 ⁺ T cells	IL-7R α and TSLPR by FACS	Enhanced expansion of CD8 ⁺ T cells activated with TCR stimulation Increased expansion of CMV-specific TCR after TCR stimulation	[63]
Human CD4 ⁺ T cells activated by TSLP-treated DCs and antigen	TSLPR and IL-7R α by image-based flow cytometry	Enhanced IL-4 expression Increase expression of CD25	[64]
Mouse in vitro Th2-polarized cells	IL-7R α by FACS TSLPR by FACS and RT-PCR	Induced expression of Bcl-2 and proliferation Increased levels of IL-4, IL-5 and IL-13	[65]
B cell progenitors			
Human fetal common myelo-lymphoid progenitor, pro-B cells	IL-7R α and TSLPR by RT-PCR and FACS	Induction of proliferation and promote human B cell differentiation from fetal hematopoietic progenitors	[66]
Innate immune cells			
Human invariant natural killer T cells	IL-7R α and TSLPR by RT-PCR, FACS and western blot	Increased expression IL-4 and IL-13	[68]
Mouse NKT cells	IL-7R α by RT-PCR TSLPR by RT-PCR and FACS	Increased expression of IL-13	[69]
Human eosinophils	IL-7R α by RT-PCR and FACS TSLPR by RT-PCR, FACS and western blot	Increased survival Increased ICAM-1, CD18, IL-6, CXCL8, CXCL1 and CCL2 expression Decreased L-selectin expression	[70]
Human mast cells derived from blood or cord blood precursors	IL-7R α and TSLPR by RT-PCR and FACS	Increased IL-5, IL-13, IL-6, GM-CSF, CXCL8 and CCL1 secretion induced by IL-1/TNF α stimulation	[32]
Mouse basophil precursor from bone marrow	IL-7R α and TSLPR by FACS	Promotion of mature basophil differentiation	[71]
Human basophil	TSLPR by FACS	Increased IL-33R expression	[71]
Mouse basophil	TSLPR by FACS	Increased basophil survival	[71]
Human type 2 innate lymphoid cells from blood or polyps	IL-7R α by FACS TSLPR by RT-PCR	Increased IL-4, IL-5, and IL-13 production	[34]
Mouse type innate lymphoid cells from ears	IL-7R α and TSLPR by FACS	Increased IL-5 and IL-13 expression	[72]

Table 2 (Continued)

Cell types	Detection methods	TSLP-mediated activity	References
Non-hematopoietic cells			
Epithelium and bronchial mucosal layers of human lungs	IL-7R α by RT-PCR and western blot. TSLPR by immunohistochemistry (IHC), RT-PCR and western blot	Increase IL-13 expression Induce bronchial epithelial cell proliferation and increased injury repair	[73]
Human airway epithelial cell line A549 and NHEBCs treated with TNF α or RSV	IL-7R α by RT-PCR and TSLPR by RT-PCR and western blot	Upregulation of CCL17 expression	[74]
Mouse epithelial cells, from jejunum, terminal ileum, and colon	TSLPR by FACS and IHC	Increase expression of the BCL-2 and SLPI	[76]
Human airway smooth muscle	IL-7R α and TSLPR by RT-PCR, FACS and IHC	Induction of IL-8/CXCL8, eotaxin-1/CCL11 and IL-6	[75]

3.4. Innate immune cells

TSLPR as well as IL-7R α were expressed by human invariant natural killer T cells in PBMCs of both AD patients or of healthy controls [68], as well as in mouse NKT cells [69]. Freshly purified human eosinophils expressed a high level of IL-7R α and a moderate level of expression of TSLPR [70]. Human mast cells exhibited a high level of TSLPR and a low level of IL-7R α in comparison with T cells [32]. Moreover, murine basophil progenitor expressed TSLPR and IL-7R α , and TSLPR was detected in basophils from human healthy donors [71]. Recently, it has been reported that freshly isolated type 2 innate lymphoid cells (ILC2) from nasal polyps or blood expressed TSLPR and IL-7R α [34], whereas TSLPR and IL-7R α were shown to be expressed in mouse ILC2 resident in skin [72].

3.5. Non-hematopoietic cells

Besides various hematopoietic cells, non-hematopoietic cells have been also reported to express TSLP receptor. Both TSLPR and IL-7R α mRNAs were detected in lung ECs isolated from bronchial biopsy specimens of asthmatic patients and healthy control subjects [73]. In addition, primary bronchial ECs from asthmatic individuals exhibited upregulated expression of TSLPR and IL-7R α following RSV infection [74]. Another report showed that human airway smooth muscle cells expressed the transcripts and proteins of TSLPR and IL-7R α [75]. Besides, intestinal epithelial cells isolated from mouse jejunum, terminal ileum, and colon expressed TSLPR [76].

Although these studies have suggested that various cells could express TSLPR or/and IL-7R α , we are still lack of knowledge on the co-expression pattern of TSLPR and IL-7R α in these different cells. It remains to be elucidated which cells (in mice and human) express functional TSLPR/IL-7R α on the cell-surface, and are bona fide targets of TSLP signal in vivo. Further studies are also required to explore how the expression and function of TSLPR/IL-7R α might be regulated in TSLP-driven immune responses.

4. TSLP-TSLP receptor signaling

The signal cascade triggered by interaction of TSLP and its functional receptor has been controversial. Initial experiments

reported that TSLP induced STAT-5 phosphorylation without the involvement of Janus kinases (JAK) [4–7,77]. However, recent studies showed that, in primary human DCs [78] and primary human and mouse CD4⁺ T cells [79], TSLP signaling led to a robust and sustained activation of JAK-1 and JAK-2. Rochman et al. raised an interesting model in which TSLPR bound and used JAK-2 in concert with IL-7R α -associated JAK-1, thereby activating STAT proteins [79]. Indeed, multiple members of STAT family have been reported in TSLP signaling using different cell lines. TSLP induced phosphorylation of STAT-5 and STAT-1 in CD4⁺ T cells [79], or that of STAT-1, -3, -4, -5 and -6 in human DCs [78]. In addition, STAT3 was found involved in TSLP signaling in primary human bronchial smooth muscle cells [75], or human trophoblast [80]. Besides, a recent study using phosphoproteomic analysis also identified that members of the Src and Tec families of non-receptor tyrosine kinases were activated upon TSLP stimulation [81].

Whereas more and more signaling molecules in TSLP signaling are being identified, how these molecules contribute to TSLP signaling related to various biological functions, under physiological or pathological conditions, have yet to be elucidated.

5. TSLP in atopic diseases

TSLP has been recognized as a key player in the pathogenesis of various human diseases, including allergy, infection, autoimmunity and cancer. Among these, the initial and most extensive studies, including ours, are in the context of atopic disorders. In this section, we summarize the implication of TSLP in AD, asthma, AR, as well as the atopic march, from four lines of evidence:

- TSLP expression in affected tissues of atopic diseases;
- TSLP gene variants associated with atopic diseases;
- the sufficiency of TSLP signaling in triggering atopic pathogenesis;
- the necessity of TSLP signaling in the pathogenesis of atopic diseases.

5.1. TSLP and AD

AD is one of the most common skin disorders seen in infants and children, characterized by pruritic, eczematoid skin lesions, with abnormal epidermal-barrier function [1,82],

affecting 15–30% in children and 2–10% in adults [1,83]. An initial link between TSLP and AD was established by Soumelis et al. [9], showing that TSLP was induced in KCs of the suprabasal layers of the epidermis of lesioned skin from acute and chronic AD patients, while it was undetectable in non-lesional skin from the same patients or in the lesions from nickel-induced contact allergic dermatitis patients or cutaneous lupus erythematosus patients. Although data from large cohorts are still lacking, serum TSLP levels in children with AD were reported to be elevated compared with healthy controls in two studies [84,85]. Another report showed that adult AD patients exhibited an increase of TSLP mRNA (in skin) and protein (in sera) compared with healthy controls [86]. Moreover, patients with Netherton syndrome, which exhibit severe AD-like phenotype with itching skin, elevated serum IgE levels and sensitization to common allergens, showed elevated TSLP expression in the skin [87].

Genetic analysis indicated that variants in TSLP and its receptors (TSLPR and IL-7R α) were associated with the risk of AD and eczema herpeticum (a rare but serious complication of AD) in European American and African American subjects [88].

In vivo studies in mice have provided strong evidences that TSLP initiates AD pathogenesis. Our previous work showed that selective ablation of RXR α and RXR β in epidermal keratinocytes induced the expression of TSLP in keratinocytes, and these mutant mice developed a chronic AD-like dermatitis, associated with Th2 cytokine expression in skin, elevated serum levels of IgE as well as blood and tissue eosinophilia [37]. Moreover, transgenic K14-TSLP mice expressing TSLP under the control of human K14 promoter [37], or transgenic mice with doxycycline-induced TSLP overexpression in keratinocytes under the control of K5 promoter [89], both developed an AD-like syndrome. In addition, *intra*dermal injection of recombinant TSLP induced a skin inflammation similar to AD [90]. All these evidences indicate that the induced TSLP expression in skin is sufficient to drive an AD pathogenesis.

Recently, studies explored whether TSLP signaling is essentially required for allergic AD pathogenesis. Using a mouse model for allergic AD induced by *epicutaneous* (*e.c.*) sensitization of protein allergen ovalbumin (OVA) in barrier-impaired skin, it was shown that mice lacking TSLPR (TSLPR $^{-/-}$) developed a less severe allergic skin inflammation [91]. Using mice in which the TSLP was selectively and inducibly ablated in epidermal KCs, our recent study demonstrated that keratinocytic TSLP was essential not only for generating skin allergic inflammation and allergen-induced T helper type 2 responses, but also for developing sensitization to allergen [52].

5.2. Asthma

Asthma is a chronic lung inflammation, characterized by airway hyperactivity, and by symptoms of recurrent wheezing, coughing, and shortness of breath [92]. It currently affects approximately 10% of children and 3% of adults [2,93,94], and

remains the leading cause of hospitalization among young children. Initially, studies by *in situ* hybridization showed increased number of cells expressing TSLP mRNA in the bronchial epithelium and submucosa of airways from asthma patients, which was correlated with disease severity and the increase of Th2-attracting chemokines CCL17 and CCL22 [95,96]. Moreover, TSLP protein level was increased in airway epithelium and lamina propria of patients with asthma (particularly the severe forms); and it correlated with the severity of the disease and the expression of the Th2 cytokine IL-13 [97].

Several TSLP variants have been associated with asthma phenotype in different populations. Two variants (SNP rs3806933 and rs2289276) in TSLP promoter region were significant associated with childhood atopic and adult asthma in a Japanese population [98]. In addition, variant rs1837253 (located around 5 kb upstream of the transcription start site) was significantly associated with protection from asthma in heterogeneous population [99]. Two of these above variants (rs2289276 and rs1837253 and) have been replicated in five ethnically different populations [100]. Additional variant located in the intron 2 (rs1898671) was associated with asthma in admixed urban population [101].

Studies in mice showed that TSLP expression in the lung triggered asthmatic airway inflammation. Transgenic SPC-TSLP mice overexpressing TSLP in lung epithelial cells under the control of surfactant protein C (SPC) promoter developed a spontaneous lung inflammation, exhibiting increased total cell and eosinophil number in bronchoalveolar lavage (BAL), infiltration of Th2 cells into the lung, airway remodeling and airway hyperresponsiveness (AHR) [102]. Another report showed that *i.n.* instillation of TSLP led to a significant inflammatory infiltrate of eosinophils and lymphocytes in the BAL, an increase of Th2 cytokine expression in lungs and an elevation of serum IgE levels [103]. In addition, mice *i.n.* treated with OVA exhibited an enhanced airway inflammation when combined with instillation of TSLP or overexpression of lung TSLP [104], suggesting that lung TSLP could promote allergen-induced asthma.

The requirement of TSLP/TSLPR was investigated by a variety of mouse models; however, the results remain controversial. Initially, using a “classical” asthma experimental model induced by OVA/aluminium *intraperitoneal* (*i.p.*) sensitization and *i.n.* challenge, it was reported that TSLPR $^{-/-}$ mice were less susceptible for developing an asthmatic phenotype [60,102]. More recently, the role of TSLP/TSLPR was examined in HDM-induced experimental asthma models, which however led to different conclusions. Willard et al. showed that TSLP played a role in generating lung inflammation when high dose of HDM was administrated [105]. A recent study reported that TSLP neutralization by blocking antibody, during last two weeks of a chronic HDM-induced asthma mouse model (5 weeks HDM treatment) diminished airway cell infiltration and structural remodeling, decreased levels of Th2 cytokines in BAL fluids, and reduced AHR [106]. Togbe et al. found that TSLPR $^{-/-}$ mice developed a reduced allergic inflammation in their HDM or papain-induced models [107].

However, using an acute HDM-induced asthma mouse model, another group declared that there was no significant implication of TSLP in airway inflammation [108], because blocking TSLP signaling either by neutralizing antibody or using TSLPR^{-/-} mice, did not reduce the severity of the asthma phenotype. Taken together, the role of TSLP in asthma pathogenesis needs to be clarified. Notably, results from the studies using experimental mouse models should be carefully interpreted, by taking into consideration the pathophysiological relevance of the experimental models, including the amount of a given allergen and the administration route of allergen. It remains also to be seen whether TSLP/TSLPR signal plays different roles during the different stages of asthma pathogenesis (e.g. allergen sensitization or challenge phase) [109], or in different cell types involved in airway inflammation. Conditional knockout mice with inducible and cell-specific ablation of *TSLP* or *TSLPR* gene should be useful to address these questions.

5.3. Allergic rhinitis (AR)

AR is an inflammation of the nasal mucosal linked with an exaggerated IgE mediated hypersensitivity to common aero-allergens, such as pollen and HDM. In biopsies from patients with AR, TSLP levels in the nasal epithelium were found increased, which correlated with AR severity [110,111]. In addition, TSLP levels were also correlated with Th2 cytokine levels, eosinophil number and local IgE levels in patients with nasal polyposis, although the increase of TSLP did not correlate with the atopic status [112].

Single TSLP variant (SNP rs1837353) has been related with AR in children with asthma in three different populations [113]. However, analyses of 11 SNPs in TSLP locus in Chinese population failed to establish any association between TSLP variants and AR. However, it is notable that AR patients with co-morbid asthma, AD or other allergic disease were excluded in this study [114].

Studies using mouse model of AR supported the implication of TSLP in AR. In an AR experimental mouse model, blocking TSLP with antibodies reduced the frequency of nasal rubs, the infiltration of leukocytes and the mucus production in the nasal epithelium and submucosa [111].

5.4. Atopic march

The term “atopic march” refers to the natural history of atopic manifestations, characterized by a typical sequence of clinical symptoms and conditions appearing during certain age period and persisting over a number of years. Commonly, AD precedes the development of airways allergic diseases (asthma and/or allergic rhinitis) [3,115]: more than 50% of AD patients with moderate to severe AD develop asthma and/or allergic rhinitis at later stage, and the severity of AD appears to influence the course of respiratory allergy. Indeed, allergen sensitization, which is developed in most of AD patients, has been recognized to be an initial step and principle risk factor in the onset of the atopic march.

Studies using mouse models have provided strong evidences that TSLP plays a critical role in the atopic march. The first evidence came from our previous study [116], revealing that increased expression of TSLP in skin KCs, either by ablation of RXRs in adult mouse KCs, or upon MC903 skin topical treatment, not only triggered an AD, but also led to aggravation of an asthmatic lung inflammation when mice were concomitantly subjected to ovalbumin (OVA) *intraperitoneal* (*i.p.*) sensitization and *i.n.* challenge [116]. These data suggested that keratinocyte-produced TSLP could provide a molecular link between AD and asthma. This was supported by another study from Demehri et al. [117], showing that induced TSLP production in skin by ablation of keratinocytic RBP-j, aggravated OVA-induced airway inflammation. Furthermore, our study showed that the increased production of TSLP in KCs only during the *i.p.* sensitization phase was able to aggravate asthma [116], thus raising an hypothesis that TSLP produced by skin KCs contributes to the progression from AD to asthma through enhancing allergen sensitization.

However, the clinical relevance of these two previous studies [116,117] was not strong, because the experimental asthma mouse model based on allergen sensitization that is induced by *i.p.* injection of OVA complexed with exogenous adjuvant (aluminium hydroxide), could not mimic the “natural” sensitization that occurs in epithelia such as skin and airways [118,119]. Recently, we further explored the role of skin TSLP in the atopic march, by employing a more faithful mouse model, which involves first an *e.c.* sensitization phase by allergen treatment on barrier-impaired skin (induced by tape stripping), followed by an *i.n.* challenge phase. Our study demonstrated that keratinocytic TSLP played a crucial role in promoting *e.c.* sensitization, thereby triggering the subsequent development of the atopic march. Of particular interest, using TSLP^{over} mice in which overexpression of TSLP in keratinocytes could be induced in a dose-dependent manner, our study showed that skin TSLP levels were correlated with skin sensitization strength and asthma severity, thus providing an important evidence that skin TSLP could promote allergic asthma in a quantity-dependent manner [52].

Besides the effect of TSLP on skin sensitization, we have also investigated whether TSLP produced by skin could impact airway sensitization. Using an experimental asthma model involving airway sensitization and challenge to HDM, our study showed that in addition to be a crucial factor in allergen sensitization through the skin, TSLP produced by epidermal keratinocytes also promoted sensitization to aeroallergens through the airway, and thereby contributed to the development of allergic asthma [120].

Together, these studies demonstrate that skin TSLP plays a critical role during the allergen sensitization phase in the onset of the atopic march. It suggests that the treatment or prevention strategy of asthma targeting only airways may be insufficient, and that blocking TSLP production in skin could be therapeutically useful in preventing or limiting both skin and airway sensitization, thus halting the progress of the atopic march.

5.5. Cellular and molecular mechanism

Although it has been now well recognized that TSLP plays a critical role in the pathogenesis of atopic diseases, the underlying cellular and molecular mechanisms remain to be elucidated. On the one hand, a great number of knowledge has been accumulated on that TSLP could act on multiple immune cells involved in atopic pathogenesis; and on the other hand, how TSLP drives and coordinates the immune responses in the tissue microenvironment is not yet well understood. We give here a brief review of these two aspects.

Studies *in vitro* have suggested a major role of TSLP in the maturation and migration of DCs. Human and mouse DCs exhibited an increase of the expression of activation markers CD40, CD80, CD86 and MHCII upon the treatment of recombinant TSLP [8,60,102]. Moreover, it was demonstrated that TSLP-activated human DCs induced an inflammatory Th2 response through OX40 ligand (OX40L) [121]. In mice, OX40L expression was shown in DCs in lung-draining LNs upon the *i.n.* treatment of OVA plus TSLP, and *in vivo* blockade of OX40L inhibited TSLP-driven Th2 lung inflammation [103]. Recently, our study demonstrated that keratinocytic TSLP was essential for inducing the OX40L expression in CD11c⁺ DCs in skin-draining LNs upon *e.c.* OVA sensitization [52]. Apart from these, human TSLP was found to trigger a cell-autonomous DC migration in confined environment [122].

Besides the effects on DCs, TSLP was also reported to induce the proliferation of mouse CD4⁺ T cells under the anti-CD3 stimulation *in vitro* and to affect CD4⁺ T cell development and proliferation *in vivo* [123]. In an *in vitro* culture system, TSLP could prime Th2 differentiation in the absence of antigen presenting cells, and the treatment of CD4⁺ T cells with TSLP in the presence of TCR stimulation led to IL-4 production [124]. However, whether TSLP plays such a role *in vivo* remains to be investigated.

Moreover, TSLP appears to have effects on various innate cell types implicated in allergic response, including mast cells, NKT cells, eosinophils, basophils and innate lymphoid cells. It was shown that TSLP enhanced the production of cytokines and chemokines (IL-5, IL-13, IL-6, GM-CSF, CXCL8 and CCL1) in human mast cells induced by IL-1/TNF stimulation [32]. TSLP was able to induce the expression of IL-13 in mouse NKT cells [69] and that of IL-13 and IL-4 in human iNKT cells [68]. TSLP-treated human eosinophils exhibited an increase of expression of cytokines and chemokines (IL-6, CXCL8, CXCL1 and CCL2), as well as adhesion molecules (ICAM-1 and CD18), and presented a prolonged survival [70]. TSLP has been also shown to act directly on bone marrow resident progenitors and trigger basophil hematopoiesis [71]. Increased levels of TSLP in circulation led to peripheral basophilia [71,125]. In addition, it was shown recently that TSLP enhanced the production of Th2 cytokines (IL-4, IL-5 and IL-13) by human and mouse innate lymphoid cells [34,72].

Although these studies suggested that TSLP could potentially target various immune cells, and exert multiple functions in different stages of atopic pathogenesis, our current

knowledge has been mostly based on either the *in vitro* stimulation of a particular cell type, or at a particular snapshot time of analyses. To achieve a better mechanistic understanding of TSLP-triggered immune responses, it is important to delineate the nature of key cellular players, and how they interact and crosstalk in an *in vivo* context. Most recently, by dissecting the cellular network triggered by mouse skin TSLP, our study uncovered that TSLP-promoted IL-4 induction in CD4⁺ T cells in skin-draining lymph nodes was driven by an orchestrated “DC-T-Baso-T” cascade, which represents a sequential cooperation of DC, CD4⁺ T cells and basophils. Moreover, this study revealed that TSLP-activated DCs primes naïve CD4⁺ T cells to produce IL-3 via OX40L signaling, and demonstrated that the TSLP-OX40L-IL-3 axis played an important role in mediating Th2 priming [126]. These findings thus made a step forward towards a comprehensive understanding of the TSLP-triggered Th2 immune responses.

6. Concluding remarks

Studies in the recent ten years have achieved great progress in recognizing the key roles of TSLP in the atopic inflammation. Besides, TSLP has been also shown to exert multiple functions in physiological and pathophysiological situations, and dysregulated TSLP expression has been associated with multiple pathologies, including inflammatory bowel diseases, parasite infection, autoimmunity and cancer, although certain conclusions from these studies remain controversial. Studies should move on to achieve a better understanding of cellular and molecular mechanisms underlying the role of TSLP in physiological and pathophysiological processes, which will be helpful for designing the therapeutic or/and preventive strategies in TSLP-associated diseases.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References

- [1] Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.
- [2] Ober C, Yao T-C. The genetics of asthma and allergic disease: a 21st century perspective. *Immunol Rev* 2011;242:10–30.
- [3] Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010;105:99–106 [quiz 107–9, 117].
- [4] Levin SD, Koelling RM, Friend SL, Isaksen DE, Ziegler SF, Perlmutter RM, et al. Thymic stromal lymphopoietin: a cytokine that promotes the development of IgM+ B cells in vitro and signals via a novel mechanism. *J Immunol* 1999;162:677–83.
- [5] Ray RJ, Furlonger C, Williams DE, Paige CJ. Characterization of thymic stromal-derived lymphopoietin (TSLP) in murine B cell development in vitro. *Eur J Immunol* 1996;26:10–6.
- [6] Friend SL, Hosier S, Nelson A, Foxworthe D, Williams DE, Farr A. A thymic stromal cell line supports in vitro development of surface IgM+ B cells and produces a novel growth factor affecting B and T lineage cells. *Exp Hematol* 1994;22:321–8.
- [7] Quentmeier H, Drexler HG, Fleckenstein D, Zaborski M, Armstrong A, Sims JE, et al. Cloning of human thymic stromal lymphopoietin (TSLP) and signaling mechanisms leading to proliferation. *Leukemia* 2001;15:1286–92.
- [8] Reche PA, Soumelis V, Gorman DM, Clifford T, Liu M, Travis M, et al. Human thymic stromal lymphopoietin preferentially stimulates myeloid cells. *J Immunol* 2001;167:336–43.
- [9] Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell-mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002;3:673–80.
- [10] Kouzaki H, O'Grady SM, Lawrence CB, Kita H. Proteases induce production of thymic stromal lymphopoietin by airway epithelial cells through protease-activated receptor-2. *J Immunol* 2009;183:1427–34.
- [11] Yu HS, Angkasekwinai P, Chang SH, Chung Y, Dong C. Protease allergens induce the expression of IL-25 via Erk and p38 MAPK pathway. *J Korean Med Sci* 2010;25:829–34.
- [12] Tang H, Cao W, Kasturi SP, Ravindran R, Nakaya HI, Kundu K, et al. The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. *Nat Immunol* 2010;11:608–17.
- [13] Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat Immunol* 2008;9:310–8.
- [14] Kashyap M, Rochman Y, Spolski R, Samsel L, Leonard WJ. Thymic stromal lymphopoietin is produced by dendritic cells. *J Immunol* 2011;187:1207–11.
- [15] Li D-Q, Zhang L, Pflugfelder SC, De Paiva CS, Zhang X, Zhao G, et al. Short ragweed pollen triggers allergic inflammation through Toll-like receptor 4-dependent thymic stromal lymphopoietin/OX40 ligand/OX40 signaling pathways. *J Allergy Clin Immunol* 2011;128:1318–25.
- [16] Zheng X, Ma P, De Paiva CS, Cunningham MA, Hwang CS, Pflugfelder SC, et al. TSLP and downstream molecules in experimental mouse allergic conjunctivitis. *Invest Ophthalmol Vis Sci* 2010;51:3076–82.
- [17] Calvén J, Yudina Y, Hallgren O, Westergren-Thorsson G, Davies DE, Brandelius A, et al. Viral stimuli trigger exaggerated thymic stromal lymphopoietin expression by chronic obstructive pulmonary disease epithelium: role of endosomal TLR3 and cytosolic RIG-I-like helicases. *J Innate Immun* 2012;4:86–99.
- [18] Kato A, Favoreto Jr S, Avila PC, Schleimer RP. TLR3- and Th2 cytokine-dependent production of thymic stromal lymphopoietin in human airway epithelial cells. *J Immunol* 2007;179:1080–7.
- [19] Qiao J, Li A, Jin X. TSLP from RSV-stimulated rat airway epithelial cells activates myeloid dendritic cells. *Immunol Cell Biol* 2011;89:231–8.
- [20] Kawasaki J, Ushio H, Kinoshita H, Fukai T, Niyonsaba F, Takai T, et al. Viral infection induces thymic stromal lymphopoietin (TSLP) in human keratinocytes. *J Dermatol Sci* 2011;62:131–4.
- [21] Fontenot D, He H, Hanabuchi S, Nehete PN, Zhang M, Chang M, et al. TSLP production by epithelial cells exposed to immunodeficiency virus triggers DC-mediated mucosal infection of CD4+ T cells. *Proc Natl Acad Sci U S A* 2009;106:16776–81.
- [22] Zeuthen LH, Fink LN, Frokiaer H. Epithelial cells prime the immune response to an array of gut-derived commensals towards a tolerogenic phenotype through distinct actions of thymic stromal lymphopoietin and transforming growth factor-beta. *Immunology* 2008;123:197–208.
- [23] Kido M, Tanaka J, Aoki N, Iwamoto S, Nishiura H, Chiba T, et al. *Helicobacter pylori* promotes the production of thymic stromal lymphopoietin by gastric epithelial cells and induces dendritic cell-mediated inflammatory Th2 responses. *Infect Immun* 2010;78:108–14.
- [24] Mosconi I, Geuking MB, Zaiss MM, Massacand JC, Aschwanden C, Kwong Chung CKC, et al. Intestinal bacteria induce TSLP to promote mutualistic T cell responses. *Mucosal Immunol* 2013;6:1157–67.
- [25] Negishi H, Miki S, Sarashina H, Taguchi-Atarashi N, Nakajima A, Matsuki K, et al. Essential contribution of IRF3 to intestinal homeostasis and microbiota-mediated TSLP gene induction. *Proc Natl Acad Sci U S A* 2012;109:21016–21.
- [26] Ishibashi Y, Sugawara K, Sugita T, Nishikawa A. Secretion of thymic stromal lymphopoietin from human keratinocytes in response to *Malassezia* yeasts. *J Dermatol Sci* 2011;62:134–8.
- [27] Vu AT, Baba T, Chen X, Le TA, Kinoshita H, Xie Y, et al. *Staphylococcus aureus* membrane and diacylated lipopeptide induce thymic stromal lymphopoietin in keratinocytes through the Toll-like receptor 2-Toll-like receptor 6 pathway. *J Allergy Clin Immunol* 2010;126:985–93.
- [28] Humphreys NE, Xu D, Hepworth MR, Liew FY, Grecis RK. IL-33, a potent inducer of adaptive immunity to intestinal nematodes. *J Immunol* 2008;180:2443–9.
- [29] Zaph C, Troy AE, Taylor BC, Berman-Booty LD, Guild KJ, Du Y, et al. Epithelial cell-intrinsic IKK-beta expression regulates intestinal immune homeostasis. *Nature* 2007;446:552–6.
- [30] Park MK, Cho MK, Kang SA, Park H-K, Kim YS, Kim KU, et al. Protease-activated receptor 2 is involved in Th2 responses against *Trichinella spiralis* infection. *Korean J Parasitol* 2011;49:235–43.
- [31] Giacomini PR, Siracusa MC, Walsh KP, Grecis RK, Kubo M, Comeau MR, et al. Thymic stromal lymphopoietin-dependent basophils promote Th2 cytokine responses following intestinal helminth infection. *J Immunol* 2012;189:4371–8.
- [32] Allakhverdi Z, Comeau MR, Jessup HK, Yoon BR, Brewer A, Chartier S, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. *J Exp Med* 2007;204:253–8.
- [33] Lee HC, Ziegler SF. Inducible expression of the proallergic cytokine thymic stromal lymphopoietin in airway epithelial cells is controlled by NF-kappaB. *Proc Natl Acad Sci U S A* 2007;104:914–9.
- [34] Mjösberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, et al. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity* 2012;37:649–59.
- [35] Wilson RH, Maruoka S, Whitehead GS, Foley JF, Flake GP, Sever ML, et al. The Toll-like receptor 5 ligand flagellin promotes asthma by priming allergic responses to indoor allergens. *Nat Med* 2012;18:1705–10.
- [36] Duan W, Mehta AK, Magalhaes JG, Ziegler SF, Dong C, Philpott DJ, et al. Innate signals from Nod2 block respiratory tolerance and program T(H)2-driven allergic inflammation. *J Allergy Clin Immunol* 2010;126:1284–93 [e10].
- [37] Li M, Messaddeq N, Teletin M, Pasquali JL, Metzger D, Chambon P. Retinoid X receptor ablation in adult mouse keratinocytes generates an atopic dermatitis triggered by thymic stromal lymphopoietin. *Proc Natl Acad Sci U S A* 2005;102:14795–800.
- [38] Li M, Hener P, Zhang Z, Kato S, Metzger D, Chambon P. Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis. *Proc Natl Acad Sci U S A* 2006;103:11736–41.
- [39] Le TA, Takai T, Vu AT, Kinoshita H, Ikeda S, Ogawa H, et al. Glucocorticoids inhibit double-stranded RNA-induced thymic stromal lymphopoietin release from keratinocytes in an atopic cytokine milieu more effectively than tacrolimus. *Int Arch Allergy Immunol* 2010;153:27–34.
- [40] Ozawa T, Koyama K, Ando T, Ohnuma Y, Hatsushika K, Ohba T, et al. Thymic stromal lymphopoietin secretion of synovial fibroblasts is positively and negatively regulated by Toll-like receptors/nuclear

- factor-kappaB pathway and interferon-gamma/dexamethasone. *Mod Rheumatol* 2007;17:459–63.
- [41] Surjit M, Ganti KP, Mukherji A, Ye T, Hua G, Metzger D, et al. Widespread negative response elements mediate direct repression by agonist- liganded glucocorticoid receptor. *Cell* 2011;145:224–41.
 - [42] Larson RP, Zimmerli SC, Comeau MR, Itano A, Omori M, Iseki M, et al. Dibutyl phthalate-induced thymic stromal lymphopoietin is required for Th2 contact hypersensitivity responses. *J Immunol* 2010;184: 2974–84.
 - [43] Satou N, Ishihara K, Hiratsuka M, Tanaka H, Endo Y, Saito S, et al. Induction of thymic stromal lymphopoietin production by xylene and exacerbation of picryl chloride-induced allergic inflammation in mice. *Int Arch Allergy Immunol* 2011;157:194–201.
 - [44] Shigeno T, Katakuse M, Fujita T, Mukoyama Y, Watanabe H. Phthalate ester-induced thymic stromal lymphopoietin mediates allergic dermatitis in mice. *Immunology* 2009;128:e849–57.
 - [45] Hirasawa N, Ohsawa Y, Ishihara K, Seyama T, Hong J, Ohuchi K. Analysis of the mechanism for the development of allergic skin inflammation and the application for its treatment: establishment of a modified allergic dermatitis model in mouse ear lobes by application of 12-O-tetradecanoyl phorbol 13-acetate: putative involvement of thymic stromal lymphopoietin and roles of histamine. *J Pharmacol Sci* 2009;110: 245–50.
 - [46] Bleck B, Tse DB, Gordon T, Ahsan MR, Reibman J. Diesel exhaust particle-treated human bronchial epithelial cells upregulate Jagged-1 and OX40 ligand in myeloid dendritic cells via thymic stromal lymphopoietin. *J Immunol* 2010;185:6636–45.
 - [47] Bleck B, Tse DB, Curotto de Lafaille MA, Zhang F, Reibman J. Diesel exhaust particle-exposed human bronchial epithelial cells induce dendritic cell maturation and polarization via thymic stromal lymphopoietin. *J Clin Immunol* 2008;28:147–56.
 - [48] Nakamura Y, Miyata M, Ohba T, Ando T, Hatsushika K, Suenaga F, et al. Cigarette smoke extract induces thymic stromal lymphopoietin expression, leading to T(H)2-type immune responses and airway inflammation. *J Allergy Clin Immunol* 2008;122:1208–14.
 - [49] Smelter DF, Sathish V, Thompson MA, Pabelick CM, Vassallo R, Prakash YS. Thymic stromal lymphopoietin in cigarette smoke-exposed human airway smooth muscle. *J Immunol* 2010;185:3035–40.
 - [50] Angelova-Fischer I, Fernandez IM, Donnadieu M-H, Bulfone-Paus S, Zillikens D, Fischer TW, et al. Injury to the stratum corneum induces in vivo expression of human thymic stromal lymphopoietin in the epidermis. *J Invest Dermatol* 2010;130:2505–7.
 - [51] Oyoshi MK, Larson RP, Ziegler SF, Geha RS. Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. *J Allergy Clin Immunol* 2010;126:976–84 [e5].
 - [52] Leyva-Castillo JM, Hener P, Jiang H, Li M. TSLP produced by keratinocytes promotes allergen sensitization through skin and thereby triggers atopic march in mice. *J Invest Dermatol* 2013;133:154–63.
 - [53] Dumortier A, Durham AD, Di Piazza M, Vauclair S, Koch U, Ferrand G, et al. Atopic dermatitis-like disease and associated lethal myeloproliferative disorder arise from loss of Notch signaling in the murine skin. *PLoS One* 2010;5:e9258.
 - [54] Demehri S, Liu Z, Lee J, Lin MH, Crosby SD, Roberts CJ, et al. Notch-deficient skin induces a lethal systemic B-lymphoproliferative disorder by secreting TSLP, a sentinel for epidermal integrity. *PLoS Biol* 2008;6:e123.
 - [55] Briot A, Deraison C, Lacroix M, Bonnart C, Robin A, Besson C, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. *J Exp Med* 2009;206:1135–47.
 - [56] Pandey A, Ozaki K, Baumann H, Levin SD, Puel A, Farr AG, et al. Cloning of a receptor subunit required for signaling by thymic stromal lymphopoietin. *Nat Immunol* 2000;1:59–64.
 - [57] Park LS, Martin U, Garka K, Gliniak B, Di Santo JP, Muller W, et al. Cloning of the murine thymic stromal lymphopoietin (TSLP) receptor: formation of a functional heteromeric complex requires interleukin 7 receptor. *J Exp Med* 2000;192:659–70.
 - [58] Rimoldi M, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM, et al. Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. *Nat Immunol* 2005;6:507–14.
 - [59] Lu N, Wang YH, Wang YH, Arima K, Hanabuchi S, Liu YJ. TSLP and IL-7 use two different mechanisms to regulate human CD4+ T cell homeostasis. *J Exp Med* 2009;206:2111–9.
 - [60] Al-Shami A, Spolski R, Kelly J, Keane-Myers A, Leonard WJ. A role for TSLP in the development of inflammation in an asthma model. *J Exp Med* 2005;202:829–39.
 - [61] De Monte L, Reni M, Tassi E, Clavenna D, Papa I, Recalde H, et al. Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. *J Exp Med* 2011;208:469–78.
 - [62] Rochman I, Watanabe N, Arima K, Liu YJ, Leonard WJ. Cutting edge: direct action of thymic stromal lymphopoietin on activated human CD4+ T cells. *J Immunol* 2007;178:6720–4.
 - [63] Akamatsu T, Watanabe N, Kido M, Saga K, Tanaka J, Kuzushima K, et al. Human TSLP directly enhances expansion of CD8+ T cells. *Clin Exp Immunol* 2008;154:98–106.
 - [64] Reefer AJ, Hulse KE, Lannigan JA, Solga MD, Wright PW, Kelly LA, et al. Flow cytometry imaging identifies rare Th2 cells expressing thymic stromal lymphopoietin receptor in a “proallergic” milieu. *J Allergy Clin Immunol* 2010;126:1049–58.
 - [65] Kitajima M, Lee H-C, Nakayama T, Ziegler SF. TSLP enhances the function of helper type 2 cells. *Eur J Immunol* 2011;41:1862–71.
 - [66] Scheeren FA, van Lent AU, Nagasawa M, Weijer K, Spits H, Legrand N, et al. Thymic stromal lymphopoietin induces early human B cell proliferation and differentiation. *Eur J Immunol* 2010;40:955–65.
 - [67] Sims JE, Williams DE, Morrissey PJ, Garka K, Foxworth D, Price V, et al. Molecular cloning and biological characterization of a novel murine lymphoid growth factor. *J Exp Med* 2000;192:671–80.
 - [68] Wu WH, Park CO, Oh SH, Kim HJ, Kwon YS, Bae BG, et al. Thymic stromal lymphopoietin-activated invariant natural killer T cells trigger an innate allergic immune response in atopic dermatitis. *J Allergy Clin Immunol* 2010;126:290–9.
 - [69] Nagata Y, Kamijuku H, Taniguchi M, Ziegler S, Seino KI. Differential role of thymic stromal lymphopoietin in the induction of airway hyper-reactivity and Th2 immune response in antigen-induced asthma with respect to natural killer T cell function. *Int Arch Allergy Immunol* 2007;144:305–14.
 - [70] Wong CK, Hu S, Cheung PF, Lam CW. TSLP induces chemotactic and pro-survival effects in eosinophils: implications in allergic inflammation. *Am J Respir Cell Mol Biol* 2010;43:305–15.
 - [71] Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. *Nature* 2011;477:229–33.
 - [72] Kim BS, Siracusa MC, Saenz SA, Noti M, Monticelli LA, Sonnenberg GF, et al. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Transl Med* 2013;5:170ra16.
 - [73] Semlali A, Jacques E, Koussih L, Gounni AS, Chakir J. Thymic stromal lymphopoietin-induced human asthmatic airway epithelial cell proliferation through an IL-13-dependent pathway. *J Allergy Clin Immunol* 2010;125:844–50.
 - [74] Miazgowiec MM, Elliott MS, Debley JS, Ziegler SF. Respiratory syncytial virus induces functional thymic stromal lymphopoietin receptor in airway epithelial cells. *J Inflamm Res* 2013;6:53–61.
 - [75] Shan L, Redhu N, Saleh A, Halayko A, Chakir J, Gounni A. Thymic stromal lymphopoietin receptor-mediated IL-6 and CC/CXC chemokines expression in human airway smooth muscle cells: role of MAPKs (ERK1/2, p38, and JNK) and STAT3 pathways. *J Immunol* 2010; 184:7134–43.
 - [76] Reardon C, Lechmann M, Brüstle A, Gareau MG, Shuman N, Philpott D, et al. Thymic stromal lymphopoietin-induced expression of the endogenous inhibitory enzyme SLPI mediates recovery from colonic inflammation. *Immunity* 2011;35:223–35.
 - [77] Isaksen DE, Baumann H, Trobridge PA, Farr AG, Levin SD, Ziegler SF. Requirement for STAT5 in thymic stromal lymphopoietin-mediated signal transduction. *J Immunol* 1999;163:5971–7.

- [78] Arima K, Watanabe N, Hanabuchi S, Chang M, Sun SC, Liu YJ. Distinct signal codes generate dendritic cell functional plasticity. *Sci Signal* 2010;3:ra4.
- [79] Rochman Y, Kashyap M, Robinson GW, Sakamoto K, Gomez-Rodriguez J, Wagner K-U, et al. Thymic stromal lymphopoietin-mediated STAT5 phosphorylation via kinases JAK1 and JAK2 reveals a key difference from IL-7-induced signaling. *Proc Natl Acad Sci U S A* 2010;107:19455–60.
- [80] Pu HH, Duan J, Wang Y, Fan DX, Li DJ, Jin LP. Thymic stromal lymphopoietin promotes the proliferation of human trophoblasts via phosphorylated STAT3-mediated c-Myc upregulation. *Placenta* 2012;33:387–91.
- [81] Zhong J, Kim M-S, Chaerkady R, Wu X, Huang T-C, Getnet D, et al. TSLP signaling network revealed by SILAC-based phosphoproteomics. *Mol Cell Proteomics* 2012;11. M112.017764.
- [82] Boguniewicz M, Leung DYM. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242:233–46.
- [83] Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest* 2004;113:651–7.
- [84] Lee EB, Kim KW, Hong JY, Jee HM, Sohn MH, Kim K-E. Increased serum thymic stromal lymphopoietin in children with atopic dermatitis. *Pediatr Allergy Immunol* 2010;21:e457–60.
- [85] Yao W, Zhang Y, Jabeen R, Nguyen ET, Wilkes DS, Tepper RS, et al. Interleukin-9 is required for allergic airway inflammation mediated by the cytokine TSLP. *Immunity* 2013;38:360–72.
- [86] Alysandratos KD, Angelidou A, Vasiadi M, Zhang B, Kalogeromitros D, Katsarou-Katsari A, et al. Increased affected skin gene expression and serum levels of thymic stromal lymphopoietin in atopic dermatitis. *Ann Allergy Asthma Immunol* 2010;105:403–4.
- [87] Hovnanian A. Netherton syndrome: skin inflammation and allergy by loss of protease inhibition. *Cell Tissue Res* 2013;351:289–300.
- [88] Gao P-S, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol* 2010;125:1403–7 [e4].
- [89] Yoo J, Omori M, Gyarmati D, Zhou B, Aye T, Brewer A, et al. Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J Exp Med* 2005;202:541–9.
- [90] Jessup HK, Brewer AW, Omori M, Rickel EA, Budelsky AL, Yoon BR, et al. Intradermal administration of thymic stromal lymphopoietin induces a T cell- and eosinophil-dependent systemic Th2 inflammatory response. *J Immunol* 2008;181:4311–9.
- [91] He R, Oyoshi MK, Garibyan L, Kumar L, Ziegler SF, Geha RS. TSLP acts on infiltrating effector T cells to drive allergic skin inflammation. *Proc Natl Acad Sci U S A* 2008;105:11875–80.
- [92] Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. *Annu Rev Immunol* 2004;22:789–815.
- [93] Tattersfield AE, Knox AJ, Britton JR, Hall IP. Asthma. *Lancet* 2002;360:1313–22.
- [94] Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355:2226–35.
- [95] Ying S, O'Connor B, Ratoff J, Meng Q, Fang C, Cousins D, et al. Expression and cellular provenance of thymic stromal lymphopoietin and chemokines in patients with severe asthma and chronic obstructive pulmonary disease. *J Immunol* 2008;181:2790–8.
- [96] Ying S, O'Connor B, Ratoff J, Meng Q, Mallett K, Cousins D, et al. Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. *J Immunol* 2005;174:8183–90.
- [97] Shikotra A, Choy DF, Ohri CM, Doran E, Butler C, Hargadon B, et al. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol* 2012;129:104–11 [e1–9].
- [98] Harada M, Hirota T, Jodo AI, Hitomi Y, Sakashita M, Tsunoda T, et al. Thymic stromal lymphopoietin gene promoter polymorphisms are associated with susceptibility to bronchial asthma. *Am J Respir Cell Mol Biol* 2011;44:787–93.
- [99] He J-Q, Hallstrand TS, Knight D, Chan-Yeung M, Sandford A, Tripp B, et al. A thymic stromal lymphopoietin gene variant is associated with asthma and airway hyperresponsiveness. *J Allergy Clin Immunol* 2009;124:222–9.
- [100] Hunninghake GM, Lasky-Su J, Soto-Quirós ME, Avila L, Liang C, Lake SL, et al. Sex-stratified linkage analysis identifies a female-specific locus for IgE to cockroach in Costa Ricans. *Am J Respir Crit Care Med* 2008;177:830–6.
- [101] Liu M, Rogers L, Cheng Q, Shao Y, Fernandez-Beros ME, Hirschhorn JN, et al. Genetic variants of TSLP and asthma in an admixed urban population. *PLoS One* 2011;6:e25099.
- [102] Zhou B, Comeau MR, De Smedt T, Liggitt HD, Dahl ME, Lewis DB, et al. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol* 2005;6:1047–53.
- [103] Seshasayee D, Lee WP, Zhou M, Shu J, Suto E, Zhang J, et al. In vivo blockade of OX40 ligand inhibits thymic stromal lymphopoietin driven atopic inflammation. *J Clin Invest* 2007;117:3868–78.
- [104] Headley MB, Zhou B, Shih WX, Aye T, Comeau MR, Ziegler SF. TSLP conditions the lung immune environment for the generation of pathogenic innate and antigen-specific adaptive immune responses. *J Immunol* 2009;182:1641–7.
- [105] Willart MAM, Deswarte K, Pouliot P, Braun H, Beyaert R, Lambrecht BN, et al. Interleukin-1 α controls allergic sensitization to inhaled house dust mite via the epithelial release of GM-CSF and IL-33. *J Exp Med* 2012;209:1505–17.
- [106] Chen Z-G, Zhang T-T, Li H-T, Chen F-H, Zou X-L, Ji J-Z, et al. Neutralization of TSLP inhibits airway remodeling in a murine model of allergic asthma induced by chronic exposure to house dust mite. *PLoS One* 2013;8:e51268.
- [107] Togbe D, Fauconnier L, Madouri F, Marchiol T, Chenuet P, Rouxel N, et al. Thymic stromal lymphopoietin enhances Th2/Th22 and reduces IL-17A in protease allergen-induced airways inflammation. *ISRN Allergy* 2013;2013:971036.
- [108] Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol* 2013;131:187–200.
- [109] Jang S, Morris S, Lukacs NW. TSLP promotes induction of Th2 differentiation but is not necessary during established allergen-induced pulmonary disease. *PLoS One* 2013;8:e56433.
- [110] Mou Z, Xia J, Tan Y, Wang X, Zhang Y, Zhou B, et al. Overexpression of thymic stromal lymphopoietin in allergic rhinitis. *Acta Otolaryngol* 2008;129:297–301.
- [111] Zhu DD, Zhu XW, Jiang XD, Dong Z. Thymic stromal lymphopoietin expression is increased in nasal epithelial cells of patients with mugwort pollen sensitive-seasonal allergic rhinitis. *Chin Med J* 2009;122:2303–7.
- [112] Kimura S, Pawankar R, Mori S, Nonaka M, Masuno S, Yagi T, et al. Increased expression and role of thymic stromal lymphopoietin in nasal polyposis. *Allergy Asthma Immunol Res* 2011;3:186–93.
- [113] Bunyavanich S, Melen E, Wilk JB, Granada M, Soto-Quiros ME, Avila L, et al. Thymic stromal lymphopoietin (TSLP) is associated with allergic rhinitis in children with asthma. *Clin Mol Allergy* 2011;9:1.
- [114] Zhang Y, Song X, Zhao Y, Zhang L, Bachert C. Single nucleotide polymorphisms in thymic stromal lymphopoietin gene are not associated with allergic rhinitis susceptibility in Chinese subjects. *BMC Med Genet* 2012;13:79.
- [115] Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112:S118–27.
- [116] Zhang Z, Hener P, Frossard N, Kato S, Metzger D, Li M, et al. Thymic stromal lymphopoietin overproduced by keratinocytes in mouse skin aggravates experimental asthma. *Proc Natl Acad Sci U S A* 2009;106:1536–41.
- [117] Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol* 2009;7:e1000067.
- [118] Takeda K, Gelfand EW. Mouse models of allergic diseases. *Curr Opin Immunol* 2009;21:660–5.
- [119] Holgate S. Perspective: a human touch. *Nature* 2011;479:S22.

- [120] Jiang H, Hener P, Li J, Li M. Skin thymic stromal lymphopoietin promotes airway sensitization to inhalant house dust mites leading to allergic asthma in mice. *Allergy* 2012;67:1078–82.
- [121] Ito T, Wang YH, Duramad O, Hori T, Delespesse GJ, Watanabe N, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 2005;202:1213–23.
- [122] Fernandez M-I, Heuzé ML, Martinez-Cingolani C, Volpe E, Donnadiou M-H, Piel M, et al. The human cytokine TSLP triggers a cell-autonomous dendritic cell migration in confined environments. *Blood* 2011;118:3862–9.
- [123] Al-Shami A, Spolski R, Kelly J, Fry T, Schwartzberg PL, Pandey A, et al. A role for thymic stromal lymphopoietin in CD4(+) T cell development. *J Exp Med* 2004;200:159–68.
- [124] Omori M, Ziegler S. Induction of IL-4 expression in CD4+ T cells by thymic stromal lymphopoietin. *J Immunol* 2007;178:1396–404.
- [125] Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomini PR, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote T(H)2 cytokine-dependent immunity. *Nat Immunol* 2009;10:697–705.
- [126] Leyva-Castillo JM, Hener P, Michea P, Karasuyama H, Chan S, Soumelis V, et al. Skin thymic stromal lymphopoietin initiates Th2 responses through an orchestrated immune cascade. *Nat Commun* 2013;4:2847.
- [127] Harada M, Hirota T, Jodo AI, Doi S, Kameda M, Fujita K, et al. Functional analysis of the thymic stromal lymphopoietin variants in human bronchial epithelial cells. *Am J Respir Cell Mol Biol* 2009;40:368–74.
- [128] Kinoshita H, Takai T, Le TA, Kamijo S, Wang XL, Ushio H, et al. Cytokine milieu modulates release of thymic stromal lymphopoietin from human keratinocytes stimulated with double-stranded RNA. *J Allergy Clin Immunol* 2009;123:179–86.
- [129] Le TA, Takai T, Vu AT, Kinoshita H, Chen X, Ikeda S, et al. Flagellin induces the expression of thymic stromal lymphopoietin in human keratinocytes via Toll-like receptor 5. *Int Arch Allergy Immunol* 2011;155:31–7.
- [130] Lee KH, Cho K-A, Kim J-Y, Kim J-Y, Baek J-H, Woo S-Y, et al. Filaggrin knockdown and Toll-like receptor 3 (TLR3) stimulation enhanced the production of thymic stromal lymphopoietin (TSLP) from epidermal layers. *Exp Dermatol* 2011;20:149–51.
- [131] Xie Y, Takai T, Chen X, Okumura K, Ogawa H. Long TSLP transcript expression and release of TSLP induced by TLR ligands and cytokines in human keratinocytes. *J Dermatol Sci* 2012;66:233–7.
- [132] Ma P, Bian F, Wang Z, Zheng X, Chotikavanich S, Pflugfelder SC, et al. Human corneal epithelium-derived thymic stromal lymphopoietin links the innate and adaptive immune responses via TLRs and Th2 cytokines. *Invest Ophthalmol Vis Sci* 2009;50:2702–9.
- [133] Xu W, He B, Chiu A, Chadburn A, Shan M, Buldys M, et al. Epithelial cells trigger frontline immunoglobulin class switching through a pathway regulated by the inhibitor SLPI. *Nat Immunol* 2007;8:294–303.
- [134] He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, et al. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial cell secretion of the cytokine APRIL. *Immunity* 2007;26:812–26.
- [135] Ito T, Liu Y-J, Arima K. Cellular and molecular mechanisms of TSLP function in human allergic disorders: TSLP programs the " Th2 code " in dendritic cells. *Allergol Int* 2012;61:35–43.