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REVIEW ARTICLE

Review Series: TSLP

TSLP Expression: Cellular Sources, Triggers, and Regulatory Mechanisms

Toshiro Takai[1]

ABSTRACT

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine initially identified in the culture supernatant of a thymic stromal cell line. Highly expressed in the epidermis in skin lesions of atopic dermatitis patients, TSLP was subsequently found to be a critical factor linking responses at interfaces between the body and environment (skin, airway, gut, ocular tissues, and so on) to Th2 responses. Recent studies have revealed that various cell types other than epithelial cells and epidermal keratinocytes (such as mast cells, airway smooth muscle cells, fibroblasts, dendritic cells, trophoblasts, and cancer or cancer-associated cells) also express TSLP. Environmental factors such as Toll-like receptor ligands, a Nod2 ligand, viruses, microbes, allergen sources, helminths, diesel exhaust, cigarette smoke, and chemicals trigger TSLP production. Proinflammatory cytokines, Th2-related cytokines, and IgE also induce or enhance TSLP production, indicating cycles of amplification. Skin barrier injury, increased epidermal endogenous protease activity, and less epidermal Notch signaling, all of which have been reported in atopic dermatitis, and keratinocyte-specific loss of retinoid X receptors and treatment of skin with agonists for vitamin D receptor in mice induce TSLP production, Th2 response, or atopic dermatitis-like inflammation. The transcription factors NF-κB and AP-1, nuclear receptors, single nucleotide polymorphisms, microRNAs, and the peptidyl-proryl isomerase Pin1 regulate TSLP mRNA expression transcriptionally or posttranscriptionally. This review focuses on events upstream of TSLP production, which is critical in allergic diseases and important in other TSLP-related disorders *i.e.* production sites, cellular sources, environmental and endogenous triggers and regulatory factors, and regulatory mechanisms of gene expression.

KEY WORDS

cellular sources, endogenous triggers and regulators, environmental triggers, regulation of gene expression, thymic stromal lymphopoietin

INTRODUCTION

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine initially identified in the culture supernatant of a mouse thymic stromal cell line.[1-4] This cytokine is a critical factor linking responses at interfaces between the body and environment (skin, airway, gut, ocular tissues, and so on) to Th2 responses.[5-9] TSLP is expressed mainly by epithelial cells (ECs) and epidermal keratinocytes (KCs). Recent studies revealed that other types of cells such as mast cells, smooth muscle cells, fibroblasts, dendritic cells (DCs), trophoblasts, and cancer or cancer-associated cells also express TSLP. Information on the environmental, endogenous, and transcriptional regulatory mechanisms of TSLP expression is essential for elucidating the pathogenesis of allergic diseases and other TSLP-related disorders and for developing new approaches in prevention and therapy. This review focuses on TSLP expression including production sites, cellular sources, environmental and endogenous triggers and regulatory factors, and regulatory mechanisms of TSLP gene expression.

PRODUCTION SITES AND CELLULAR SOURCES OF TSLP

TSLP produced in response to both environmental and endogenous factors contributes to disorders

[1]Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, Tokyo, Japan.
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Correspondence: Toshiro Takai, Atopy (Allergy) Research Center, Juntendo University Graduate School of Medicine, 2–1–1 Hongo, Bunkyo-ku, Tokyo 113–8421, Japan.
Email: t–takai@juntendo.ac.jp
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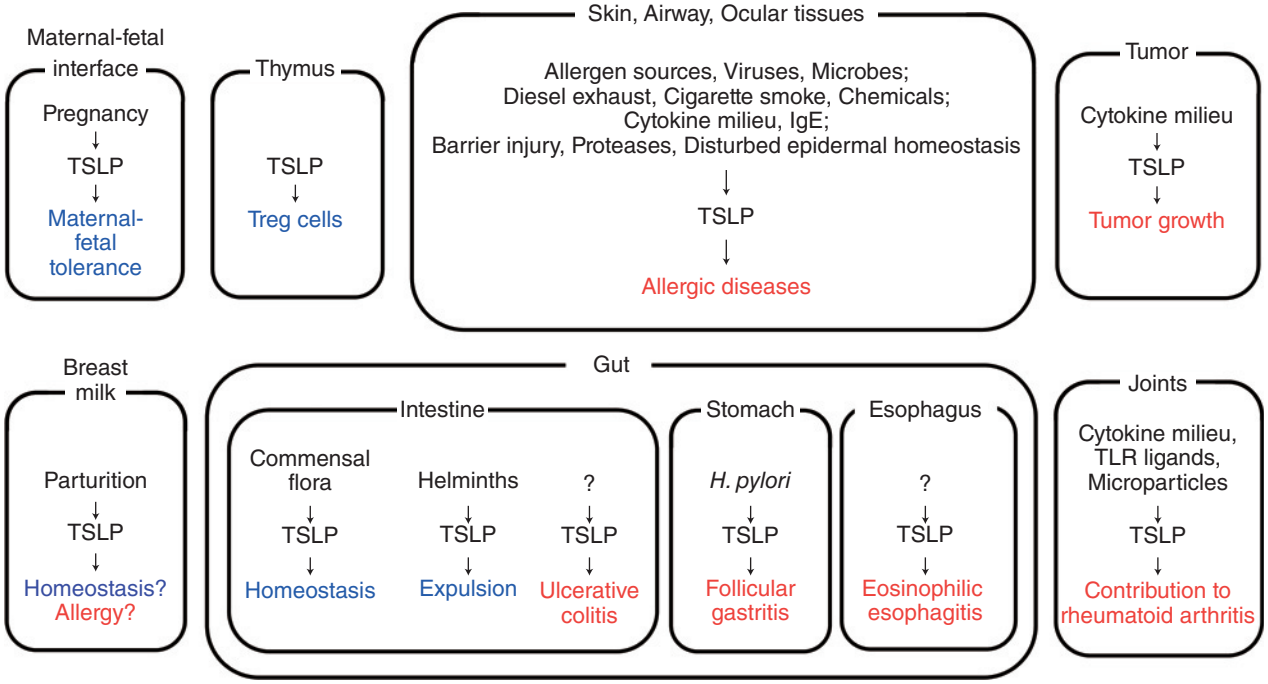

Fig. 1 TSLP produced in response to environmental and endogenous factors contributes to disorders and homeostasis. TSLP is expressed mainly by epithelial cells (ECs) and keratinocytes (KC) at barrier surfaces and is constitutively expressed in the thymus and intestinal ECs. TSLP expression in the epidermis, epithelium, and submucosa in skin, airway, and ocular tissues plays a critical role in the pathogenesis of allergic diseases. Constitutive expression in the human thymus is responsible for the differentiation of Treg cells, and that in intestinal ECs via interaction with intestinal commensal microflora may contribute to intestinal homeostasis, a loss of which is observed in patients with Crohn disease. TSLP expressed in trophoblasts may contribute to maternal-fetal tolerance. TSLP expression in the tumor microenvironment contributes to tumor growth. TSLP expressed in synovial fluid may have a role in rheumatoid arthritis. *Red*: Disorders. *Blue*: Homeostasis.

and homeostasis (Fig. 1). TSLP is expressed mainly by ECs and KCs at barrier surfaces. Its expression in the epidermis, epithelium, and submucosa in skin, airway, and ocular tissues plays a critical role in the sensitization process and exacerbation of allergic diseases. An initial analysis by real-time quantitative PCR in a panel of cDNA libraries from different cells or cell lines and a panel of purified primary cells indicated that KCs, ECs, smooth muscle cells, and lung fibroblasts, cultured in growth medium and stem cell-derived mast cells activated by cross-linking of high-affinity IgE receptors (FcεRI) express TSLP mRNA in large amounts.[10] Airway smooth muscle cells (ASMCs) activated by IL-4, IL-13, and TNF-α and KCs activated by TNF-α and IL-1β expressed higher TSLP mRNA levels than cells cultured in medium alone. Recent studies also have reported that not only KCs and ECs but also various other cell types can express TSLP mRNA and/or protein (Fig. 2).

THYMUS

TSLP was initially identified in the culture supernatant of the mouse thymic stromal cell line Z210R.1.[1,2] In human thymus, TSLP is selectively expressed by ECs of Hassall's corpuscles within the thymic medulla.[11] The constitutive expression is responsible for the differentiation of Treg cells by modulating the activity of thymic DCs.

GUT

Taylor *et al*.[12] reported that TSLP is expressed constitutively in intestinal ECs, with its highest levels in colonic ECs. Primary intestinal ECs from healthy subjects but not patients with Crohn disease constitutively expressed TSLP.[13,14] The TSLP expressed in intestinal ECs may be involved in tolerance to commensal microflora through modulation of DC function. Inflamed mucosal lesions from ulcerative colitis patients had higher levels of TSLP mRNA than uninflamed mucosa and normal controls.[15] Cultured human intestinal ECs produced TSLP without stimuli[13] or in response to stimulation *in vitro*.[16]

TSLP immunoreactivity is detected in mucosal lesions from patients with *Helicobacter pylori*-infected follicular gastritis.[17] Human gastric ECs produce TSLP in response to stimuli *in vitro*.[17]

TSLP mRNA was overexpressed in esophagal biopsy samples from individuals with eosinophilic esophagitis.[18] Human esophageal ECs expressed TSLP mRNA in response to stimulation *in vitro*.[19]

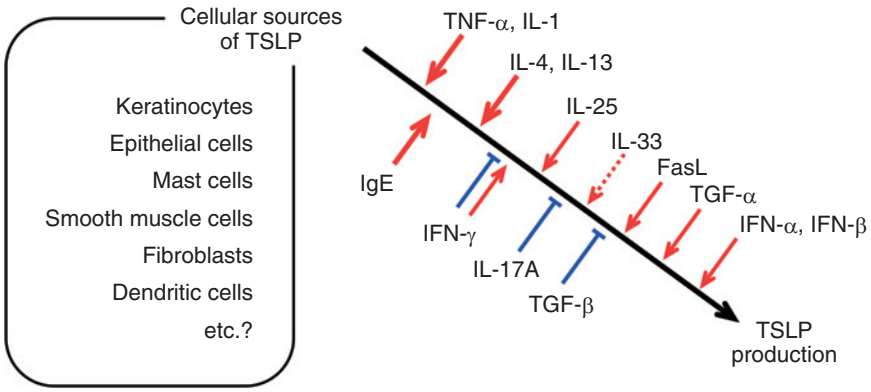

Fig. 2 Regulation of TSLP expression by cytokines and IgE. Positive and negative regulation (induction of TSLP mRNA or protein expression, and enhancement or inhibition of TSLP expression by other stimuli) is shown (see text). Positive effects of pro-inflammatory cytokines (TNF-α and IL-1) and Th2 cytokines (IL-4 and IL-13) are observed in various cell types. Cross-linking of FcεRI-bound IgE induces TSLP expression in mast cells and IgE without cross-linking induces TSLP expression in airway smooth muscle cells (ASMCs). Promotion of TSLP expression by IgE and Th2-related cytokines (IL-4, IL-13, IL-25, and IL-33) indicates amplification cycles. Some reports described inhibitory effects of IFN-γ in keratinocytes, epithelial cells, and fibroblasts but a report described that IFN-γ enhanced TSLP expression induced by a combination of TNF-α and IL-4 in intestinal epithelial cells. *Red*: Promotion. *Blue*: Inhibition. *Broken line*: Possible indirect regulation *in vivo*.

BREAST MILK

TSLP is present in human breast milk.[20] The cellular source is assumed to be mammary ECs. The potential roles of breast milk TSLP in the development of the neonatal gastrointestinal tract and of allergies in childhood remain to be determined.

AIRWAY

Ying *et al.*[21,22] reported TSLP mRNA expression in bronchial epithelium and submucosa in cytokeratin$^+$ ECs, CD31$^+$ endothelial cells, tryptase$^+$ mast cells, elastase$^+$ neutrophils, and CD68$^+$ macrophages in patients with asthma and chronic obstructive pulmonary disease (COPD). Consistent with their results, a recent report described that TSLP immunostaining in bronchial epithelium was localized predominantly to ECs, although occasional mast cells, macrophages, and neutrophils were identified.[23] Conversely, Okayama *et al.*[24] reported that 90% of bronchial mucosal TSLP protein$^+$ cells are mast cells. Zhang *et al.*[25] reported TSLP immunoreactivity in airway smooth muscle (ASM) bundles from patients with COPD. Cultured human lung ECs,[26,27] mast cells,[24] ASMCs,[25] and bronchial fibroblasts,[28] produce TSLP in response to stimulation *in vitro*.

Higher concentrations of TSLP in nasal lavage[29] and higher levels of TSLP expression in nasal ECs[30] of patients with allergic rhinitis than the control group have been reported. Mou *et al.*[31] reported TSLP immunoreactivity in the pseudostratified ciliated columnar epithelium of nasal mucosa in patients with allergic rhinitis and additional staining in subepithelial inflammatory cells. Kimura *et al.*[32] observed TSLP immunoreactivity in ECs, endothelial cells, fibroblasts, and inflammatory cells in nasal polyps and nasal mucosa and that the number of TSLP$^+$ cells was greater in nasal polyps than nasal mucosa in patients with allergic rhinitis. Cultured human nasal ECs[29] and nasal polyp fibroblasts[33] produce TSLP in response to stimuli *in vitro*.

Soumelis *et al.*[10] found TSLP immunoreactivity in crypt ECs of human inflamed tonsils and a few small foci of TSLP expression within the apical part of the squamous epithelium.

A recent study reported that mouse lung CD11c$^+$ DCs expressed TSLP mRNA at an even higher level than did epithelial cells when the animals were challenged with house dust mite extract.[34] GM-CSF-induced mouse bone marrow-derived myeloid DCs, primary mouse splenic DCs, human monocyte-derived DCs, and human peripheral blood monocytes express TSLP mRNA and/or produce TSLP in response to stimulation *in vitro*.

SKIN

Soumelis *et al.*[10] found TSLP to be expressed in KCs of the apical layers of the epidermis in skin lesions of acute and chronic atopic dermatitis (AD) patients but not in nonlesional skin and not in lesions of patients with nickel-induced allergy contact dermatitis or cuta-

neous lupus erythematosus. Human skin explants,[35] cultured epidermal KCs,[36] and dermal fibroblasts[37] produce TSLP in response to *in vitro* stimuli. Increased serum TSLP levels in children with AD,[38] but not in adults,[39,40] have been reported, although a report described increased serum TSLP concentrations in patients with AD including adults.[41]

A report described that dermal TSLP expression was induced at 1 hour after an allergen challenge in the skin of allergic rhinitis and/or asthma patients in elastase$^+$ neutrophils, CD31$^+$ endothelial cells, tryptase$^+$ mast cells, and CD68$^+$ macrophages.[42]

OCULAR TISSUES

Matsuda *et al*.[43] reported TSLP expression in conjunctival ECs of giant papillae from patients with chronic allergic keratoconjunctivitis (vernal keratoconjunctivitis or atopic keratoconjunctivitis). Cultured conjunctival ECs,[44] corneal ECs, and corneoscleral tissues[45] produce TSLP in response to stimulation *in vitro*.

MATERNAL-FETAL INTERFACE

Guo *et al*.[46] reported that human trophoblasts and decidual ECs at the maternal-fetal interface of early placentas express TSLP mRNA and protein, but only trophoblasts secrete soluble TSLP. The study suggests that human trophoblasts may contribute to maternal-fetal tolerance.

TUMOR MICROENVIRONMENT

Recent papers reported that TSLP expression in the tumor microenvironment contributes to tumor growth following intratumoral Th2 cell differentiation.[37,47] A report described increased serum TSLP levels in patients with cutaneous T cell lymphomas.[40]

SYNOVIAL FLUID

Koyama *et al*.[48] reported higher TSLP concentrations in synovial fluid from patients with rheumatoid arthritis than those with osteoarthritis and showed a contribution of TSLP to an experimental arthritis in mice. Synovial fibroblasts from patients with rheumatoid arthritis and those with osteoarthritis produces similar amounts of TSLP in response to *in vitro* stimuli.[48,49] Microparticles isolated from synovial fluids induced the release of TSLP in synovial fibroblasts from patients with rheumatoid arthritis.[50]

ENVIRONMENTAL TRIGGERS FOR TSLP PRODUCTION

At barrier interfaces, environmental stimuli trigger TSLP production (Fig. 1). Allergen exposure, viral infections, microflora, helminth infections, diesel exhaust, cigarette smoke, and chemicals trigger TSLP production, resulting in initiation of the sensitization process and the exacerbation of allergic diseases. Induction of TSLP production through interaction with intestinal commensal microflora may contribute to intestinal homeostasis.

TLR LIGANDS

Primary human airway ECs release TSLP in response to Toll-like receptor (TLR) ligands: synthetic double-stranded RNA (dsRNA) (polyinosinic-polycytidylic acid, polyI:C) (TLR3 ligand), mimicking viral dsRNA, in small airway ECs[26] and bronchial ECs[27]; and peptideglycan (PGN) (TLR2 ligand) and lipoteicoic acid (LTA) (TLR2 ligand) in small airway ECs.[26] Bronchial ECs from patients with asthma are biased towards higher TSLP and lower IFN-β production in response to polyI:C.[51] A report described induction of low TSLP mRNA expression by LTA, poly(CpG) (TLR8 ligand), and CpG-B (TLR9 ligand) in primary human bronchial ECs.[52] Combinations of ovalbumin and low or high concentrations of LPS induce TSLP mRNA expression in primary mouse stroma cells.[53]

Primary human KCs[36,54-56] and corneal ECs[45] release TSLP in response to polyI:C, diacylated lipopeptide FSL-1 (TLR2-TLR6 ligand), and flagellin (TLR5 ligand). Human corneoscleral tissues produce TSLP in response to polyI:C *ex vivo*.[45] Primary human conjunctival ECs express TSLP mRNA and release TSLP in response to polyI:C.[43,44]

Primary human oral ECs release TSLP in response to polyI:C.[57] Primary human esophagus ECs express increased TSLP mRNA levels in response to polyI:C[19]; and human esophagus EC lines, in response to polyI:C and zymosan (TLR2-TLR6 ligand).[58] The human colonic EC line Caco-2 expressed TSLP mRNA in response to polyI:C[15] and flagellin.[59]

Primary human synovial fibroblasts release TSLP in response to polyI:C and LPS.[49] DCs have been reported to produce TSLP in response to TLR ligands.[34] Mouse bone marrow-derived myeloid DCs release TSLP in response to CpG (TLR9 ligand), LPS, and zymosan and express TSLP mRNA in response to flagellin. Primary mouse splenic DCs express TSLP mRNA in response to CpG and LPS. Human peripheral blood monocytes and monocyte-derived DCs produce TSLP in response to zymosan and LPS.

Nod2 LIGAND

Intracellular nucleotide-binding oligomerization domain (Nod)-like receptors (NLRs) belong to another class of pattern recognition receptors. Nod1 and Nod2 detect motifs of bacterial peptideglycans. Mesodiaminopimelic acid (meso-DAP) expressed by most gram-negative bacteria and muramyl dipeptide (MDP) expressed by most gram-positive and gram-negative bacteria are ligands for Nod1 and Nod2, respectively. Intranasal administration of the Nod2 ligand, but not the Nod1 ligand, rapidly induced lung expression of TSLP mRNA in mice, with a peak at 3 hours.[60]

VIRUSES

Rhinovirus RV16 induced TSLP mRNA expression in primary human bronchial ECs[27] and stimulated the release of TSLP in bronchial ECs from COPD patients.[61] Respiratory syncytal virus (RSV) enhanced TSLP production in primary rat airway ECs.[62] Influenza A virus increased the amount of TSLP in the supernatant of cocultures of nasal ECs from smokers and monocyte-derived DCs from nonsmokers.[63] Vesicular stomatitis virus (VSV) induced the release of TSLP in primary human KCs.[64]

Human immunodeficiency virus (HIV) triggered TSLP production in a human cervical EC line, C33, and TSLP mRNA expression in several human EC lines (neuronal SKMN and intestinal HT-29) and primary KCs, but not in other cell types such as fibroblasts and T cells.[65] In rhesus macaques, simian immunodeficiency virus (SIV) causes dramatic increases in TSLP production concurrent with an increase in viral replication in the vaginal tissues.[65]

MICROBES

An important contribution of *Staphylococcus aureus*, which heavily colonizes the lesions of AD patients, to the pathogenesis of AD has been suggested. An *S. aureus* membranous fraction stimulated the release of TSLP in primary human KCs and the induction of TSLP mRNA expression was dependent on TLR2 and TLR6 mRNA expression, suggesting that *S. aureus*-derived diacylated lipoproteins trigger TSLP production.[55] *S. aureus*-derived extracellular vesicles promoted the release of TSLP in primary mouse dermal fibroblasts.[66] *Malassezia* yeasts, which are also members of the cutaneous microflora and act as an exacerbating factor in AD, stimulated the release of TSLP in primary human KCs, an effect inhibited by competitive antagonists for lysophosphatidic acid (LPA) receptors.[67]

Both live and dead microorganisms stimulated the release of TSLP in a human colonic EC line, Caco-2.[16,68] Direct contact with *Helicobacter pylori* promoted the release of TSLP in the human gastric EC lines, MKN45 and MKN28.[17] TSLP immunoreactivity was detected in mucosal lesions from patients with *H. pylori*-infected follicular gastritis.[17]

ALLERGEN SOURCES

Allergen sources such as house dust mites, pollens, fungi, and insects produce or contain proteases.[69] Kouzaki *et al*.[70] reported that prototypic proteases, trypsin (serine protease) and papain (cysteine protease), and an extract of the airborne fungus *Alternaria* stimulated release of TSLP in a human bronchial epithelial cell line, BEAS-2B. The upregulation of TSLP gene expression in BEAS-2B cells was inhibited by transfection with protease-activated receptor-2 (PAR2) siRNA completely for trypsin and partially for papain and the *Alternaria* extract. They also described that trypsin, papain, the *Alternaria* extract and a PAR2 agonist peptide induced TSLP mRNA expression in primary human bronchial ECs. Yu *et al*.[71] reported that papain induced TSLP mRNA expression in a mouse lung epithelial cell line MLE12 and primary mouse lung ECs; a mite major allergen Der p 1 with cysteine protease activity in MLE12 cells and mouse embryonic fibroblasts (MEFs); and an *Aspergillus oryzae* protease in MEFs. Tang *et al*.[72] reported that the injection of papain into mouse ears induced TSLP expression in the epidermis, which was dependent on reactive oxygen species (ROS), TLR4, and TRIF. Sokol *et al*.[73] described that papain induced TSLP mRNA expression in mouse bone marrow-derived basophils.

Airway administration of house dust mite extract in mice induces release of TSLP into bronchoalveolar lavage fluid in a manner dependent on TLR4 expression in airway structural cells.[74] However, a recent report described that lung $CD11c^+$ DCs expressed TSLP mRNA at an even higher level than did ECs in mice challenged intratracheally with house dust mite extract.[34] Administration of ragweed pollen extract to mouse ocular surfaces induced TSLP production in corneal and conjunctival epithelia[75,76] and the release of TSLP in primary human conjunctival ECs, both in a TLR4-dependent manner.[75] In a human skin equivalent model, active scabies mites *Sarcoptes scabiei* on the surface and scabies mite extract induced the release of TSLP.[77]

Chitin is a polysaccharide providing structural rigidity to fungi, mites, insects, helminths, crustaceans, and so on, many of which are allergen sources. Chitin stimulated primary human KCs and a human KC line HaCaT to release TSLP.[78]

HELMINTHS

Infections of mice with the intestinal-dwelling nematode *Trichuris muris* result in upregulated TSLP mRNA expression in the intestine.[79] Helminths produce proteases and chitin,[80] which as well as allergen-derived proteases may induce TSLP expression as described above. A recent report described that *Trichinella spirals* excretory proteins stimulated TSLP mRNA expression in a mouse colon EC line, CT-26, which was partially prevented by a serine protease-specific protease inhibitor.[81]

DIESEL EXHAUST PARTICLES

Diesel exhaust particles (DEPs) stimulate the release of TSLP in primary human bronchial ECs and mRNA expression in a human bronchial EC line, 16HBE $14o^-$.[82,83] DEPs increase ROS production, and DEP-induced TSLP mRNA expression can be inhibited by an antioxidant, N-acetyl cysteine (NAC).[82]

CIGARETTE SMOKE EXTRACT

Intranasal administrations of cigarette smoke extract

(CSE) in mice induce TSLP production mainly in bronchial ECs.[84] The CSE-induced TSLP production can be inhibited by intraperitoneal administration of NAC. CSE stimulates TSLP production in primary human ASMCs, and the reduction in CSE-induced TSLP production by NAC is partial.[85]

CHEMICALS

In mice, the treatment of skin with aromatic compounds[86] and dibutyl phthalate (DBP)[87] induced TSLP production in the epidermis. Intraperitoneal administration of diisononyl phthalate (DINP) enhanced TSLP expression induced in the ears by intradermal injection with house dust mite extract.[88] Among the aromatic compounds tested, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, and xylene are volatile solvents of paints and glues and are often detected in indoor environments. DBP is a commonly used plasticizer and also used as an additive in adhesives or printing inks. DINP is a principal plasticizer in various polyvinyl chloride products.

12-*O*-tetradecanoylphorbol 13-acetate (TPA), also known as phorbol myristate acetate (PMA), induces TSLP production in the epidermis in mice.[89] TPA/PMA plus A23187 induced TSLP mRNA expression in a human mast cell line, HMC-1.[90] TPA/PMA is known as a tumor promoter. A23187 is a calcium ionophore.

ENDOGENOUS TRIGGERS AND REGULATORS

Proinflammatory cytokines, Th2-related cytokines, and IgE contribute to TSLP production, suggesting amplification cycles (Fig. 2). TSLP production can be positively or negatively regulated via nuclear receptors and β2-adrenoceptor signaling, although the mechanisms have not been fully elucidated.

Skin barrier injury, increased epidermal endogenous protease activity, and less epidermal Notch signaling, all of which have been reported in AD, and as well as the KC-specific loss of retinoid X receptors, treatment of skin with agonists for the vitamin D receptor in mice induce TSLP production and, in mice, a Th2 response or AD-like inflammation, demonstrating that a disturbance of epidermal homeostasis triggers TSLP production and the increase in TSLP concentrations in the epidermis induces the onset of Th2 inflammation.

Regulation by microRNAs (miRNAs) of TSLP production in intestine and skin has been reported. The peptydil-proryl isomerase Pin1, which maintains the structure and activity of transcription-related proteins, also contributes to TSLP production.

CYTOKINES

Cytokines can induce, enhance, or suppress TSLP production (Fig. 2). In primary human small airway ECs, a combination of IL-1β and TNF-α stimulated the release of TSLP.[26] In primary human bronchial ECs, a combination of TNF-α with Th2 cytokines (IL-4 or IL-13) stimulated the release of a small amount of TSLP, and IL-4 or IL-13 promoted the polyI:C-induced release of TSLP.[27] In a human bronchial EC line, BEAS2B, IL-4 and IFN-γ respectively enhanced and inhibited the release of TSLP induced by trypsin, papain, *Alternaria* extract, and polyI:C.[70] In the mouse lung EC line MLE12, IL-25 (also known as IL-17E), which is an initiator cytokine of Th2 responses,[7] stimulated TSLP mRNA expression.[91]

In human primary nasal ECs, IL-25 and IL-17A enhanced and inhibited the polyI:C-induced release of TSLP, respectively.[29] In primary human nasal polyp fibroblasts, TNF-α induced the release of TSLP; IL-4 or IL-13 enhanced the TNF-α-induced the release of TSLP; and IFN-γ inhibited the relase of TSLP induced by TNF-α plus IL-4 or IL-13.[33] In mice, IL-13 induced TSLP production in nasal epithelium *ex vivo* and *in vivo*.[92]

In primary human ASMCs, TNF-α, IL-1α, IL-1β, and mast cell-derived TNF-α, but not IL-4 and IL-13, induce the release of TSLP, and IL-1β enhances the TNF-α-induced release of TSLP.[25,93] A report described that IL-4 induces the release of TSLP in primary human bronchial ECs; TNF-α in primary human ASMCs and lung fibroblasts: and a combination of IL-4 and TNF-α induces the highest concentration of TSLP released in the three types of lung tissue cells.[28]

Proinflammatory cytokines (TNF-α or IL-1α) with Th2 cytokines (IL-4 or IL-13) acted synergistically to induce TSLP production in human skin explants.[35] In primary human KCs, a combination of TNF-α and Th2 cytokines stimulated TSLP production and promoted the release of TSLP induced by polyI:C, FSL-1, *S aureus* membrane, and flagellin.[36,55,56] Type I IFNs (IFN-α and IFN-β) enhanced polyI:C-induced TSLP production.[36] IFN-γ, TGF-β, and/or IL17A inhibited TSLP production induced by polyI:C, FSL-1, and *S. aureus* membrane.[36,55] TGF-α, a ligand for the epidermal growth factor receptor (EGFR), upregulated flagellin-induced TSLP production.[56] A report described that Fas ligand (FasL) induces TSLP mRNA expression in reconstituted human epidermis.[94] Netherton syndrome patients infused with the anti-TNF-α antibody Infliximab exhibited an improvement in AD-like symptoms and decrease of TSLP production in skin.[95] KC-specific transgenic expression of IL-13 in mice induced TSLP production in KCs and AD-like phenotypes.[96]

In primary human corneal ECs, TNF-α and IL-1β induced the release of TSLP, and Th2 cytokines (IL-4 or IL-13) promoted the release of TSLP induced by TNF-α, polyI:C, or flagellin.[45] In human corneoscleral tissues, TNF-α induces release of TSLP, and Th2 cytokines (IL-4 or IL-13) upregulate release of TSLP induced by TNF-α or polyI:C *ex vivo*.[45]

In a human colonic EC line, Caco-2, a combination of TNF-α and IL-4 induced TSLP mRNA expression which was enhanced by IFN-γ, resulting in production of the TSLP protein.[15] In another human colonic EC line, HT-29, IL-13 induced the expression of the miRNA miR-375, which is responsible for TSLP mRNA and protein production.[97] Intraperitoneal injection of IL-33, an initiator cytokine of the Th2 response,[7] enhanced *Trichuris muris* (nematode)-induced TSLP mRNA expression in the intestine of mice.[79]

In human mast cells, priming with IL-4 enhances TSLP mRNA expression induced by cross-linking of high-affinity IgE receptor (FcεRI)-bound IgE, resulting in enhanced TSLP production.[24] In GM-CSF-induced mouse bone marrow-derived DCs, IL-4 augmented TSLP production induced by CpG, LPS, and zymosan.[34] GM-CSF plus IL-4-induced human monocyte-derived DCs produce TSLP in response to zymosan and LPS.

In primary human cancer-associated fibroblasts, TNF-α, IL-1β, and tumor-derived TNF-α and IL-1β caused the release of TSLP, but had little or no effect in primary human dermal fibroblasts from normal skin.[37] In primary human synovial fibroblasts, TNF-α induced TSLP production[48] and IFN-γ inhibited TSLP production induced by TNF-α, LPS, or polyI:C.[49]

IgE

In peripheral blood-derived mast cells, cross-linking of FcεRI-bound IgE induces TSLP mRNA expression and priming with IL-4 augments it, resulting in enhanced TSLP production.[24] Mast cell-derived proteases, the majority of which are released within 1 hour after FcεRI aggregation, degrade the TSLP released, making the detection of TSLP in culture supernatant difficult.[24] Human ASMCs express FcεRI. Interestingly, in primary human ASMCs, stimulation with IgE without being cross-linked with anti-IgE antibodies or allergens induces the release of TSLP and the induction of TSLP mRNA expression is dependent on spleen tyrosine kinase (Syk).[98] These reports suggest that IgE-TSLP exacerbates allergic diseases (Fig. 2).

IgA

In the human intestinal EC line Caco-2 grown as polarized monolayers, the association of *Lactobacillus* or *Bifidobacterium* with nonspecific secretory IgA enhanced probiotic adhesion and potentiated TSLP production.[99]

LIPID MEDIATORS

Lysophosphatidic acid (LPA) is a bioactive lipid-mediator, levels of which are elevated in the lungs of patients with asthma. LPA induces the release of TSLP in primary human bronchial ECs in a manner dependent on CARMA3/CARD10, a protein containing a caspase recruitment domain (CARD).[100]

Endogenous and synthetic agonists for EP3 [a subtype of prostaglandin E2 (PGE2) receptors], PGE2 and ONO-AE248, inhibit polyI:C-induced release of TSLP in human conjunctival ECs.[101] Previous studies demonstrated that the PGE2-EP3 pathway suppresses allergic airway inflammation and contact hypersensitivity in mice.

REGULATION VIA β2-ADRENOCEPTOR SIGNALING

β2-adrenoceptor agonists (β2-agonists) including two long-acting agonists (salmeterol and formoterol) and a short-acting agonist (salbutamol) enhance the release of TSLP induced by a combination of IL-4 and TNF-α via upregulation of intracellular cAMP in primary bronchial ECs, ASMCs, and lung fibroblasts,[28] while salmeterol inhibits the polyI:C-induced release of TSLP in primary human bronchial ECs.[102]

REGULATION VIA NUCLEAR RECEPTORS

Nuclear receptors belong to a superfamily of ligand-dependent transcriptional regulators that include ligand-dependent and orphan receptors. Within the nuclear receptor superfamily, the retinoid X receptor (RXR) isotypes (RXRα, β, and γ) play a key role as heterodimeric partners for other nuclear receptors, e.g. retinoic acid receptors (RARs), vitamin D receptor (VDR), peroxisome proliferator-activated receptors, and liver X activated receptor. In mice, epidermal KC-specific ablation of genes for RXRα and RXRβ,[103] as well as treatment of skin with physiologically active ligands for VDR [1,25-dihydroxyvitamin D_3 (the active form of vitamin D_3; calcitriol) and its analog MC903 (calcipotriol; Dovonex)],[104,105] results in increased TSLP production in the skin and an AD-like phenotype (Fig. 3, *upper*). 9-*cis*-retinoic acid (9-*cis*-RA), a RXR agonist, inhibited IL-1β-induced TSLP mRNA expression in a human bronchial EC line, $16HBEo^-$ cells.[106]

Glucocorticoids (GCs), ligands of the GC receptor (GR), can inhibit TSLP production (Fig. 3, *upper*).[27,49,107-109] A combination of GC and a long acting β2-agonist, salmeterol, synergistically inhibited the polyI:C-induced release of TSLP in primary human bronchial ECs.[102] GC can inhibit the release of TSLP induced by cytokines plus salmetelol.[28] A GC response element (GRE) in mouse TSLP promoter can act as a silencer element.[109]

BARRIER DYSFUNCTION

Skin barrier dysfunction is a critical driving force in the initiation and exacerbation of AD and the "atopic march" in allergic diseases.[69,110-112] Injury to the stratum corneum in human skin with tape stripping or a detergent, sodium lauryl sulfate, induces TSLP production in the epidermis.[113] Injury with tape stripping in mice induces TSLP production in skin, which po-

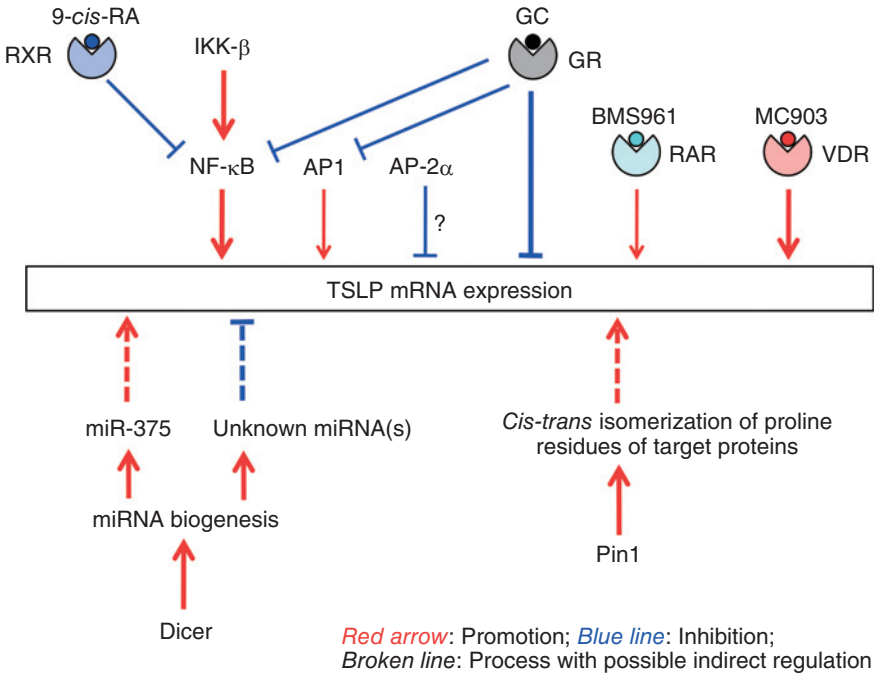

Fig. 3 Transcriptional and posttranscriptional regulation of TSLP mRNA expression. *Upper*: Transcriptional regulation by transcription factors (NF-κB, AP-1, and AP-2α) and nuclear receptors (RXR, VDR, RAR, and GR). The regulation by RXR-RAR heterodimers and RXR-VDR heterodimers, both in complexes with corepressors, in the model proposed by Li *et al.*[104] is not represented here (see text). *Lower*: Posttranscriptional and/or transcriptional regulation by microRNAs (miRNAs) and Pin1. TSLP production in intestine and skin seems to be differently (positively or negatively, respectively) regulated by miRNAs (see text). *GC*, Glucocorticoid; *GR*, GC receptor; *RAR*, Retinoic acid receptor; *RXR*, Retinoid X receptor; *VDR*, Vitamin D receptor; *9-cis-RA*, RXR agonist; *BMS961*, RARγ agonist; *MC903*, VDR agonist.

larizes skin DCs to elicit a Th2 response.[114]

A report described that knockdown of the expression of filaggrin, a stratum corneum structural protein essential for skin barrier function, in the human KC cell line HaCaT and reconstituted human epidermal layers enhanced polyI:C-induced TSLP production.[115]

Knockdown of the expression of E-cadherin, an adhesion molecule that mediates intercellular contact through homophilic interactions, in the human bronchial EC line 16HBE 14o$^-$ induced the mRNA expression of TSLP and TARC through EGFR signaling pathways.[116]

ENDOGENOUS PROTEASES

Netherton syndrome is a severe genetic skin disease with constant atopic manifestations that is caused by mutations in *SPINK5* (serine protease inhibitor Kazal-type 5), which encodes lymphoepithelial Kazal-type related inhibitor (LEKTI).[117,118] A lack of LEKTI causes SC detachment secondary to epidermal protease hyperactivity[119] and overexpression of TSLP.[120] LEKTI inhibits the protease activity of epidermal kallikrein (KLK) 5, KLK7, and KLK14.[121] KLK5 directly activates PAR2 to upregulate TSLP mRNA expression and induces TSLP production in primary human KCs.[120] At embryonic day 19.5, *Spink5/Par2* double knockout mice display a dramatic decrease in TSLP expression, confirming the role of the KLK5-PAR2 cascade in TSLP-mediated early proallergic signaling.[122] Levels of the transcription factor Sp1 were significantly decreased in skin biopsy samples obtained from patients with AD.[123] Knockdown of Sp1 expression in primary human KCs caused the upregulation of KLK-related genes including KLK5, and the elevated KLK activity induced TSLP production.[124]

Channel-activating protease-1 [CAP1; also termed protease serine S1 family member-8 (Prss8)], the mouse homologue of human prostasin, is a glycosylphosphatidylinositol (GPI)-anchored serine protease. KC-specific transgenic expression of either CAP1/Prss8 or PAR2 in mice causes an AD-like-disease associated with increased TSLP expression and the former is dependent on PAR2 expression.[125] CAP1/Prss8 can trigger PAR2-dependent signaling

but cannot directly activate PAR2. The CAP1/Prss8-induced signaling is dependent on intermediate activation of another serine protease, pro-CAP3/martiptase, which in turn is a remarkably potent and specific activator of PAR2.

NOTCH SIGNALING

The Notch signaling pathway is a critical regulator of epidermal integrity. Patients with AD but not psoriasis or lichen planus have a marked reduction of Notch receptor expression in the skin.[126] KC-specific ablations of Notch signaling lead to higher TSLP concentrations and AD-like disease in mice.[126-128]

miRNAs

miRNAs have emerged as important regulators of many biological processes.[129,130] In a human colorectal cancer cell line, HT-29, IL-13 induces the miRNA miR-375, which induces TSLP mRNA and protein production, indicating a Th2-amplification loop.[97] In mice, abolishing the induction of miRNAs by inducible gut-specific ablation of *Dicer1*, which encodes Dicer, an enzyme involved in miRNA biogenesis, results in lower levels of colon epithelial TSLP mRNA.[97]

Inducible epidermal KC-specific ablation of *Dicer1* in mice results in an aggravated MC903-induced AD, accompanied by an increase in TSLP production by KCs.[131] Skin of the mice with ablation of *Dicer1* also shows increased TSLP production upon topical treatment with DBP. Thus, TSLP production in intestine and skin seems to be differently regulated by miRNAs (Fig. 3). Identifying miRNAs implicated in the skin and other epithelia needs to be addressed.

PEPTIDYL-PRORYL ISOMERASE Pin1

Eukaryotic transcription is regulated predominantly by the posttranslational modification of the participating components. One such modification is the *cis-trans* isomerization of peptidyl-proryl bonds by the peptidyl-proryl isomerase Pin1 (Fig. 3, *lower panel*), resulting in a conformational change in the protein involved.[132] Targets of Pin1 include proteins involved in transcription or posttranscriptional steps.[132,133] In rats sensitized and challenged with ragweed pollen, the intraperitoneal administration of juglone, a Pin1 inhibitor, decreased lung TSLP and bronchoalveolar lavage cell TNF-α mRNA expression.[133] In primary mouse lung fibroblasts, juglone inhibited TSLP mRNA and protein expression induced by IL-4 plus TNF-α.

TRANSCRIPTIONAL REGULATION OF TSLP GENE EXPRESSION

NF-κB activation is considered essential for TSLP production (Fig. 3).[52,134] According to the data obtained by luciferase reporter assays, binding of the transcription factor NF-κB (and also AP-1 in cultured human ASMCs[98,135]) in humans and mice around -3.8 kb upstream of the *TSLP* transcription initiation site is essential for inducible TSLP gene expression in lung ECs.[52,106] However, the regulation of TSLP gene expression on the chromatin structure by nuclear receptors is more complex and has not been fully elucidated.[103,104,106,109] Two single nucleotide polymorphisms (SNPs) in the human TSLP promoter, which are associated with disease susceptibility to asthma, are located in transcription factor-binding motifs and affect the binding of transcription factors to the sites.[102,136]

NF-κB REGULATORY REGION AROUND -3.8 KB 5' UPSTREAM OF THE *TSLP* TRANSCRIPTION INITIATION SITE

Lee *et al*.[52] concluded that inducible human and mouse TSLP gene expression requires activation of NF-κB and subsequent binding to a site around -3.8 kb upstream of the transcription initiation site (hereafter called the "NF-κB regulatory region") on the basis of the data obtained by reporter assays using human TSLP promoter-containing luciferase reporter plasmids. ~120 bp of the human TSLP gene promoter from -3.74 to -3.86 kb upstream of the transcription initiation site contained a *cis* element that was required for IL-1β-induced promoter activity in the human bronchial EC line 16HBEo$^-$. The ~120 bp sequence contained consensus binding sites for the transcription factors NF-κB, IRF-1, and Opaque-2, and a putative binding site for AP-1. Mutation of the NF-κB motif significantly decreased the IL-1β-induced promoter activity; mutation of the putative AP-1 motif partially lowered the activity; and mutation of the IRF-1 or the Opaque-2 motif had no effect. A region from -3.6 to -3.8 kb upstream of the mouse *TSLP* transcription initiation site, which contains two putative NF-κB motifs, was required for inducible promoter activity in the mouse lung EC line MLE12. Mutation of the 3' NF-κB site, but not the 5' site, eliminated IL-1β-mediated induction of the promoter activity. This study also examined the deletion of two putative RXR-binding sites upstream of the mouse TSLP gene [base pairs -2175 to -2164 (DR1) and base pairs -1062 to -1049 (DR2), which are predicted by Li *et al*.[103]] and found the deletion constructs to have no effect on the promoter activity in the reporter plasmids.[52] Li *et al*.[104] described the presence of putative NF-κB-binding sites in the human and mouse TSLP gene promoter (one for the human promoter and two for the mouse promoter), however, they were located at different sites from those in the human and mouse NF-κB regulatory regions reported by Lee *et al*..[52]

Redhu *et al*.[98,135] demonstrated that mutation of the NF-κB or putative AP-1 motif in the ~120 bp of the human TSLP gene promoter significantly decreased both TNF-α-induced and IgE-induced promoter activities in primary human ASMCs. The roles of the IRF-1 and Opaque-2 motifs[52] in the human NF-κB regula-

tory region are unknown.

REGULATION VIA RXR

Li *et al*.[103] demonstrated that, in mice, epidermal KC-specific ablation of genes for the nuclear receptors RXRα and RXRβ results in increased TSLP production in the skin and an AD-like phenotype. In another paper,[104] they proposed that RXR to be involved in directly repressing transcription through the binding of the RXR-VDR-corepressor complex and RXR-RARγ-corepressor complexes to the mouse TSLP promoter.

Lee *et al*.[106] found that 9-*cis*-RA, an agonist for RXR, inhibited IL-1β-induced human TSLP mRNA expression in 16HBEo$^-$ cells. In the presence of 9-*cis*-RA, RXR bound to IL-1β-induced NF-κB and prevented it from binding to oligonucleotide probes containing the NF-κB consensus motif or the NF-κB binding site in the human TSLP promoter. Chromatin immunoprecipitation (ChIP) assays revealed that 9-*cis*-RA can block the recruitment of NF-κB to the endogenous TSLP promoter. In the presence or absence of 9-*cis*-RA, the binding of RXR to the putative retinoic acid responsive element (RARE) in the endogenous human TSLP promoter (-3912 to -3900) was not detected by the ChIP assay. These results indicate that 9-*cis*-RA-bound RXR acts to repress IL-1β-induced TSLP gene expression by preventing NF-κB from binding to the promoter through the binding of 9-*cis*-RA-liganded RXR to NF-κB, *i.e.* inhibition of NF-κB activation by 9-*cis*-RA occurs at the level of NF-κB (Fig. 3, *upper*) and not at the human TSLP promoter, contrary to the model proposed by Li *et al*..[104]

ACTIVATION BY VDR AGONISTS

Li *et al*.[104,105] demonstrated that, in mice, skin treatment with the active form of vitamin D_3 or its analog MC903, agonists for VDR, results in increased TSLP production in the skin and an AD-like phenotype. They suggested that VDR is involved in directly repressing transcription through binding of the unliganded VDR-RXR heterodimer to the mouse TSLP promoter and that the topical application of the VDR agonists generates RXR-VDR-coactivator complexes whose transcriptional activity is efficient enough to not only relieve the repression exerted by RXR-RARγ-corepressor complexes but also to further enhance the basal promoter activity.[104] Interestingly, cotreatment with a RARγ-selective agonist (BM961) (Fig. 3, *upper*) and a limiting dose of the active form of vitamin D_3 synergistically enhanced the TSLP gene expression in mouse skin, supporting the model.[104]

REPRESSION VIA GR

GC can inhibit TSLP production.[27,49,107-109] Although GR-mediated transrepression was generally ascribed to indirect "tethered" interaction with other DNA-bound regulators, such as NF-κB and AP1, Surjit *et al*.[109] reported that GC transcriptionally repressed TSLP expression in AD mouse models and demonstrated the repression to be mediated through the direct binding of GR to a simple negative GC response element (GRE) (Fig. 3, *upper*), which belongs to a novel family of evolutionary-conserved *cis*-acting negative response elements (IR nGREs) found in numerous GC-repressed genes. ChIP assays revealed that binding of GC-liganded GR to the mouse TSLP IR nGRE (IR1 nGRE) (-1352 to -1343) enables the formation of a repressing complex containing SMRT and NCoR corepressors. Generation of the repressing complex on the IR1 nGRE precludes the MC903-induced or all-*trans*-RA (a RAR agonist)-induced formation of an activating complex including SRC-2 (and also SRC-3 upon MC903 treatment) and RNA polymerase II in DR3d vitamin D response element (VDRE) (-7370 to -7356), DR2b RARE (-13893 to -13880), and proximal promoter (PP) (-318 to -8) regions. The mouse TSLP IR1 nGRE located -1.3 kb upstream from the PP region can act as a silencer element precluding the formation of a chromatin loop between the PP and the DR3d VDRE enhancer region located -7.3 kb upstream.

SPLICING FORMS

In primary human bronchial ECs, two forms of *TSLP* (long and short) have been reported and polyI:C upregulates the expression of long-form *TSLP* and induces release of TSLP.[136] The role of the human short-form *TSLP* is unknown.

FUNCTIONAL ANALYSIS OF SNPs

Harada *et al*.[102,136] found that the promoter SNPs rs3806933 and rs2289276 are significantly associated with disease susceptibility in both childhood atopic and adult asthma. They demonstrated that rs3806933 (-847 C > T), which creates a binding site for AP-1, affects the transcriptional efficiency of the long-form *TSLP* induced by polyI:C in primary human bronchial ECs.[136] They also found that rs2289276 (-82 C/T) is located in a binding motif of AP-2α, a possible transcription suppression factor, and demonstrated higher AP-2α binding to -82 C, which may have reduced the transcriptional activity through repressive effects on transcription.[102]

SUMMARY

TSLP is expressed mainly by ECs and KCs at barrier surfaces and is constitutively expressed in the thymus and intestinal ECs (Fig. 1). TSLP expression in the epidermis, epithelium, and submucosa in skin, airway, and ocular tissues plays a critical role in the pathogenesis of allergic diseases. TSLP constitutively expressed in the human thymus is responsible for the differentiation of Treg cells. TSLP constitutively expressed in intestinal ECs via interaction with intestinal commensal microflora may contribute to intestinal homeostasis, a loss of which is observed in pa-

tients with Crohn disease. Recent studies reported that various cell types such as mast cells, ASMCs, fibroblasts, and DCs can express TSLP. TSLP expressed in trophoblasts may contribute to maternal-fetal tolerance. TSLP expression in the tumor microenvironment contributes to tumor growth. TSLP expressed in synovial fluid may have a role in rheumatoid arthritis.

At barrier interfaces, environmental stimuli such as allergen sources, viruses, microbes, helminths, diesel exhaust, cigarette smoke, and chemicals trigger TSLP production, resulting in initiation of the sensitization process and the exacerbation of allergic diseases (Fig. 1). Proinflammatory cytokines, Th2-related cytokines, and IgE contribute to TSLP production (Fig. 2), indicating an amplification cycle for the Th2 response. TSLP production can be positively or negatively regulated via nuclear receptors and β2-adrenoceptor signaling. Skin barrier injury, increased endogenous protease activity, less Notch signaling, loss of RXRα and RXRβ expression, and VDR agonists induce TSLP production and, in mice, a Th2 response or AD-like inflammation, demonstrating that a disturbance of epidermal homeostasis triggers TSLP production and increase in TSLP concentrations in the epidermis induces the onset of Th2 cytokine-associated inflammation. Regulation of TSLP expression by microRNAs and peptidyl-proryl isomerase Pin 1 has been reported (Fig. 3, *lower*). The transcription factors NF-κB and AP-1 contribute to TSLP gene expression (Fig. 3, *upper*). Nuclear receptors such as RXRs, RARs, VDR, and GR regulate TSLP gene expression in the chromatin. Two promoter SNPs associated with asthma, which respectively affect binding of the transcription factors AP-1 and AP-2α, have been reported. Studies of environmental, endogenous, transcriptional and posttranscriptional regulatory mechanisms of TSLP expression will contribute to the elucidation of the pathogenesis of allergic diseases and other TSLP-related disorders and to the development of new approaches in prevention and therapy.

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