*Current Perspective***Exacerbation of Allergic Diseases by Chemicals: Role of TSLP**Ryosuke Segawa¹ and Noriyasu Hirasawa^{1,*}¹Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Miyagi 980-8578, Japan

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Abstract. Environmental chemicals, such as cigarette smoke and diesel exhaust, have been reported as risk factors that exacerbate allergic diseases. However, the exacerbation mechanisms induced by these chemicals are not yet fully understood. Thymic stromal lymphopoietin (TSLP) is produced mainly by epithelial cells and plays an important role as a master switch of allergic inflammation because it promotes Th2-type immune responses by inducing the activation of dendritic cells. Chemical compounds, such as formalin, have been shown to bind to proteins and form a new antigen that induces allergic responses. A second group of chemicals that enhance allergic responses to exogenous proteins have also been reported. We recently demonstrated that some of these chemicals induced TSLP production and may potentially augment Th2-type allergic responses. We proposed that TSLP-producing chemical compounds should be recognized as chemical allegro-accelerators.

Keywords: thymic stromal lymphopoietin, environmental chemical, allergy

1. Introduction

The prevalence of allergic diseases such as atopic dermatitis, bronchial asthma, and allergic rhinitis has increased. Allergic diseases are characterized by inflammation with excessive Th2-type immune responses to harmless substances. The induction and severity of these diseases are known to be affected by both genetic factors and environmental factors. For example, as a genetic factor, loss-of-function variants of filaggrin, which induces changes in the epithelial permeability of allergens, have been associated with atopic dermatitis (1). Air pollution, an example of an environmental factor, has been shown to enhance sensitization to allergens and Th2-type immune responses (2). Complex mixtures of chemicals such as diesel exhaust also represent exacerbation factors for allergic disorders in the environment (2).

Chemical compounds, such as formalin, have been demonstrated to bind to proteins and form a new antigen that induces allergic responses. Such chemicals are called contact antigens. A second group of chemicals that enhance allergic responses to exogenous proteins have

also been reported. The first cells to be exposed to exogenous chemicals are the epithelial cells lining the surface of the body, and these cells have been shown to be the main producers of thymic stromal lymphopoietin (TSLP), which is a master cytokine to the Th2-type immune responses induced as described below. We and others recently reported several chemicals induced TSLP production and could contribute to Th2 skewing. We proposed that such kinds of chemicals be referred to as chemical allegro-accelerators. Here we provide an overview of the roles of TSLP in allergic diseases and the chemicals that induce the production of TSLP.

2. TSLP

TSLP is a member of the IL-2 cytokine family and is also a paralog of IL-7. Murine TSLP was discovered in a thymic stromal cell line supernatant that promoted B cell development (3). Human TSLP was isolated using a database search method and this gene was mapped to chromosome 5q22.1, which is closely located to the Th2 cytokine gene cluster loci 5q23-32. Murine and human TSLP share poor sequence homology (only 43% amino acid identity) but a significant degree of functional homology. TSLP was reported to induce signals through a heterodimer of the IL-7 receptor alpha chain (IL-7R α) and TSLP-receptor subunit (TSLPR) (4, 5). Functional

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TSLPRs are expressed mainly on DCs and also hematopoietic cells including T cells, B cells, granulocytes, and mast cells. TSLP has been shown to promote the expression of OX40 ligand and activation of dendritic cells (DCs). The TSLP-primed DCs skew Th2-dominant immune responses via production of Th2 chemokines, such as thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC), and induction of naïve CD4⁺ T cells that produce Th2 cytokines, such as IL-4, -5, and -13, and the inflammatory cytokine TNF- α (6, 7). Furthermore, TSLP enhances the production of Th2 cytokines by TNF- α and IL-1 α -stimulated human mast cells (8). Hence, TSLP is a key molecule to skew Th2-type immune responses.

Consistent with the other members of the IL-2 cytokine family, TSLP is known to induce the activation of Janus kinase (JAK) and signal transducer and activator of transcription (STAT). A previous study demonstrated that recombinant TSLP stimulated JAK1 and JAK2 phosphorylation in human myeloid DCs and subsequently phosphorylated STAT1, 3, 4, 5, and 6 (9). On the other hand, TSLP activated JAK1 and JAK2 in murine and human primary CD4⁺ T cells and induced the phosphorylation of STAT5 only (10). Thus, TSLP induces different signals depending on the type of cell and also exerts multiple functions.

3. Contribution of TSLP to allergic disease

The crucial roles of TSLP in allergic inflammation were demonstrated using transgenic and gene-knockout mice. For example, the skin-specific overexpression of TSLP caused atopic dermatitis-like skin inflammation (11). In an ovalbumin (OVA)-induced allergic asthma model of mice, asthmatic responses were markedly attenuated in TSLPR-knockout mice (12). TSLP has also been implicated in human diseases. Shikotra et al. reported that the expression of TSLP was increased in the airway epithelia and lamina propria of severely asthmatic patients (13). Soumelis et al. also reported that TSLP expression was increased in the lesional skin of atopic dermatitis patients, but not in non-lesional skin, the lesional skin of patients with nickel-induced contact dermatitis, or lupus erythematosus patients (4).

Genome-wide association studies revealed the association between TSLP and human allergic diseases. A single nucleotide polymorphism in the TSLP promoter region of the TSLP gene has been associated with bronchial asthma (14). Chromosome 5q22, which contains the *TSLP* gene, is a candidate locus of asthma (1) and eosinophilic esophagitis (EoE), which is characterized by the allergic-induced abnormal infiltration of eosinophils in the esophagus (1). The expression of TSLP in esophageal

biopsies was significantly higher in EoE patients than in normal individuals, and TSLP expression levels were correlated with the variant at chromosome 5q22 (1). These findings indicate that TSLP may serve as a therapeutic target molecule.

4. Regulation of TSLP production

Regulation of the production and action of TSLP is summarized in Fig. 1. TSLP is produced mainly by barrier surface cells such as airway epithelial cells (ECs) and keratinocytes in the epidermis. In addition, recent studies have indicated that other types of cells such as mast cells, DCs, smooth muscle cells, and fibroblasts also produce TSLP (15). TSLP production is also known to be induced by exogenous and endogenous factors (15). Toll-like receptor (TLR) ligands are the major inducers of TSLP production. Allakhverdi Z et al. reported that TLR2 agonists, bacterial proteoglycan (PGN), and lipoteichoic acid (LTA), and the TLR3 agonist poly I:C upregulated TSLP production (8). TLR ligand-induced TSLP production was shown to be further regulated by Th2 and Th1 cytokines, namely, enhanced by IL-4 and IL-13 and attenuated by IFN- γ (16). Inflammatory cytokines, such as TNF- α and IL-1 β , and some proteases have been identified as endogenous triggers for TSLP production. TNF- α was shown to induce TSLP production by activating the transcription factors NF- κ B and activator protein-1 (AP-1) in human smooth muscle cells (17). Several proteases also induce TSLP production through protease-activated receptor 2, the most appropriate example of which is Netherton syndrome (NS), a severe skin disease with atopic symptoms. In NS patients, a mutation in the *serine protease inhibitor Kazal-type 5* gene encoding the Lympho-epithelial Kazal-type-related inhibitor leads to the excessive activation of kallikrein 5, resulting in the expression of TSLP in keratinocytes via the activation of protease-activated receptor 2 (18).

One of the features of TSLP expression is hormonal regulation. TSLP production was previously shown to be either positively or negatively regulated by several nuclear receptors such as the retinoid X receptor (RXR) (19), vitamin D receptor (20), and glucocorticoid receptor (21). Thus, various exogenous and endogenous factors affect TSLP production.

5. TSLP-producing chemicals

Some chemical compounds have recently been shown to stimulate TSLP production both in vivo and in vitro (Table 1). In the following sections, we summarized recent studies on chemical compound-induced TSLP

Fig. 1. Production and role of TSLP in the exacerbation of allergic inflammation by environmental chemicals.

production and its roles in the exacerbation of allergic inflammation.

5.1. 12-*O*-Tetradecanoylphorbol 13-acetate (TPA)

TPA is a potent tumor promoter found in coal tar and activates protein kinase C. We previously demonstrated that painting TPA on mouse ear lobes induced TSLP expression (22). TPA painting after sensitization with picryl chloride shifted the cytokine milieu from Th1 to Th2 (22). Thus, TSLP production has been implicated in TPA-induced changes in immune responses.

In an in vitro system, we also revealed that TPA induced TSLP production in the mouse keratinocyte cell line PAM212 (unpublished data). The human mast cell line HMC-1 was confirmed to produce TSLP upon stimulation with TPA. The costimulation of TPA and calcium ionophores was shown to upregulate TSLP production via the caspase-1/NF- κ B pathway (23).

5.2. Diesel exhaust particles

Diesel exhaust particles (DEPs) are one of the components of air pollution. In an experimental asthma model using *Dermatophagoides farinae* allergens (Der f), the

injection of DEPs with Der f enhanced the production of Th2 cytokines, eosinophil infiltration, and airway remodeling (24). Although it has not yet been clarified whether DEP-induced TSLP influences the exacerbation of these allergic manifestations in vivo, Bleck et al. reported that DEPs induced TSLP production in human bronchial epithelial cells (HBECs) (25, 26). Furthermore, a co-culture of HBECs with DCs in the presence of DEPs promoted the expression of OX40L and TARC in DCs, and activated DCs subsequently increased the proliferation of T cells. These responses were inhibited by TSLP siRNA transfection to HBECs, which indicated that TSLP produced by HBECs plays a role in the activation of DCs (25, 26). A recent study demonstrated that microRNA-375 also regulated DEP-induced but not TNF- α -induced TSLP production in HBECs (27). This is the first report to suggest a relationship between microRNA and chemical compound-induced TSLP production.

5.3. Cigarette smoke extract (CSE)

Exposure to cigarette smoke and its components is also a risk factor that augments the allergic inflammation

Table 1. List of TSLP-producing chemicals

Chemicals	Structure	Producing tissue or cell	References
12- <i>O</i> -tetradecanoyl phorbol 13-acetate (TPA)		Ear tissue (<i>m</i>) MC line (<i>h</i>)	(22) (23)
Diesel exhaust particles	Not defined	Bronchial EC line (<i>m</i>)	(25 – 27)
Cigarette smoke extract	Not defined	Bronchial EC (<i>m</i>) ASM cell line (<i>h</i>)	(28) (31)
Dibutyl phthalate		Ear tissue (<i>m</i>) KC line (<i>m</i>)	(32) (33)
Xylene Trimethylbenzene		Ear tissue (<i>m</i>)	(34)
Medium-chain fatty acids (heptanoic, octanoic, and Nonanoic acids)		Eat tissue (<i>m</i>)	(35)

MC: mast cell, EC: epithelial cell, ASM: airway smooth muscle, KC: keratinocyte, *m*: mouse, *h*: human.

Table 2. Indoor average concentrations of the main environmental chemicals in Japan in 1997

Chemicals	Average indoor conc. ($\mu\text{g}/\text{m}^3$)
Ethanol	281.2
Toluene	93.3
Acetone	32.3
1,2,4-Trimethylbenzene	29
<i>m</i> -Xylene	26.7
Limonene	26.5
Decane	23.1
Ethylbenzene	21.6
Nonane	20.9
Undecane	14.6
α -Pinene	12.9
Octane	11.5
<i>o</i> -Xylene	11.5
Butyl acetate	10.3
1,3,5-Trimetyl benzene	9.6

associated with asthma and rhinitis. In the OVA-induced allergic asthma model of mice, repeated intranasal exposure to CSE induced TSLP production in bronchial epithelial cells. The administration of an anti-TSLP antibody to the same model attenuated CSE-enhanced

leukocyte infiltration and the production of OVA-specific IgE and Th2 cytokines in the lung (28). CSE-induced TSLP expression was shown to be abolished by *N*-acetylcysteine, an anti-oxidant, and also in TNF- α receptor 1-knockout mice. *N*-Acetylcysteine also abrogated CSE-induced TNF- α production. These findings suggest that CSE induced TSLP production in vivo via oxidative stress and TNF- α receptor 1 activation. Oxidative stress leads to the activation of NF- κ B (29), which is involved in the expression of TSLP. Oxidative stress also induced the production of oxidized lipids, which triggered TSLP production via stimulating TLR4 (30).

CSE was shown to increase the expression of TSLP and TSLPR mRNA in human airway smooth muscle (ASM) cells, and this response was not attributed to nicotine or ROS (31). Thus, the molecular mechanisms by which CSE induces TSLP production remain unclear.

5.4. Dibutyl phthalate (DBP)

DBP is an airborne pollutant derived from industrial activity and has also been suggested to be an adjuvant for experimental allergic models. Shigeno et al. demonstrated that DBP induced TSLP production, which was required in the sensitization and elicitation phases for the migration of antigen-presenting cells to the lymph nodes and ear swelling in a fluorescein isothiocyanate

(FITC)-induced contact hypersensitivity model (32). The development of Th2-type responses induced by FITC and DBP was shown to be markedly decreased in TSLPR-deficient mice (33). However, although DBP also induced TSLP expression in an in vitro system using PAM212 mouse keratinocytes (33), the mechanism of DBP recognition by keratinocytes and intracellular signaling in TSLP production have yet to be clarified.

5.5. Xylene and trimethylbenzene

Table 2 shows the indoor average concentrations of major environmental chemicals in Japan in 1997. We examined the ability of environmental chemicals to induce TSLP production by painting on the ear lobes of mice and showed that exposure to xylene, especially *m*-xylene, and trimethylbenzene induced TSLP production (34). Xylene and trimethylbenzene are component of paints and glues, and both have been detected at relatively high concentrations in the indoor environment (Table 2), which suggests that exposure to these compounds occurs easily. Xylene was shown to aggravate picryl chloride-induced thickening of the ear and IL-4 production, both of which were attenuated in TSLPR-deficient mice (34), indicating that xylene-induced TSLP affected immune responses. TSLP immunostaining revealed the presence of TSLP-producing cells in epithelial tissues. Xylene-induced TSLP production was not reduced in mast cell-deficient mice (34), which demonstrated that mast cells were not a main source of TSLP. Interestingly, xylene-induced TSLP production appeared to be diminished in both TNF- α -knockout mice and IL-4-knockout mice. These findings suggest that xylene induced TSLP production in epithelial tissues, possibly in keratinocytes, in a manner dependent on TNF- α and IL-4. *m*-Xylene was shown to induce TSLP production more potently than *o*-xylene, suggesting that these effects were not due to the non-specific action of an organic solvent. The molecular mechanisms of recognition of *m*-xylene are currently being investigated.

5.6. Medium-chain fatty acid

Medium-chain fatty acids are components of several natural soaps and are used as additive agents in cigarettes and herbicides. We demonstrated that medium-chain fatty acids, especially heptanoic, octanoic, and nonanoic acids, induced TSLP production in vivo (35). In addition, painting nonanoic acid, as well as xylene, on mouse ear lobes enhanced ear thickening in picryl chloride-induced allergic inflammation. This enhancement was attenuated in TSLPR-deficient mice (35). The sensitization with OVA was also enhanced by nonanoic acid (35). Since nonanoic acid may be a hydrolysate of vanillylnonanamide (36), which is an analog of capsaicin, and included

in topical pain medications, exposure to nonanoic acid may occur when these medications are used.

6. Conclusions and further perspectives

Various environmental chemical compounds are known to induce TSLP production and aggravate allergic diseases via TSLP signaling (Fig. 1). We proposed that such chemical compounds should be recognized as chemical allegro-accelerators. These findings also indicate that TSLP signaling is a promising target in the treatment of allergic diseases, and its inhibition may prevent the exacerbation of allergic symptoms by various chemicals. However, the components in a chemical mixture that induce the production of TSLP and how chemical compounds are recognized and induce TSLP production have not yet been determined. Elucidation of these questions will contribute to understanding individual differences in sensitivity to environmental chemicals and the development of preventative strategies against the exacerbation of allergic diseases by environmental chemicals.

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