



Mini Review

Induction of thymic stromal lymphopoietin by chemical compounds in vivo and exacerbation of allergy

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Exposure to several chemical compounds in the environment might worsen allergies. However, it remains unclear which chemicals except for contact-sensitizing compounds modify inflammatory and immune responses and how. Thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine produced mainly by epithelial cells, plays important roles in the initiation of allergic inflammation. We found that the painting of xylene on ear lobes induced production of TSLP and exacerbated the picryl chloride-induced allergic dermatitis. Thus, there are chemical compounds in the environment which do not have contact-sensitizing activity but cause the production of TSLP and on exacerbation of allergic dermatitis.

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Introduction

Atopic dermatitis is an allergic inflammatory disease characterized by intense pruritus, chronic eczematous plaques, and relapsing inflammation induced by repeated exposure to the antigen. In the inflamed skin, infiltration by eosinophils, the number of mast cells, and Th2-type immune responses are generally increased^{1,2}. It is important to prevent exacerbation of the inflammation, from scratching for example, which can destroy the barrier function of skin and worsen the dermatitis. In addition, exposure to chemical compounds in the environment might exacerbate allergies. However, it remains unclear which chemicals other than contact-sensitizing compounds modify inflammatory and immune responses and how. Therefore, it is necessary to establish a suitable experimental model to identify chemical compounds which worsen allergic dermatitis and to clarify the molecular mechanisms involved.

Experimental models of allergic dermatitis

At present, there are several animal models of dermatitis with atopic dermatitis-like skin lesions. For example, repeated epicutaneous exposure to contact-sensitizing compounds such as 2,4,6-trinitro-1-chlorobenzene^{3,5} and paraphenylenediamine⁶, or dust mite allergen⁷ results in chronic contact hypersensitivity. NC/Nga mice have also been used as a model of atopic dermatitis⁸⁻¹⁰. The contact hypersensitivity induced by contact-sensitizing compounds is caused by Th1-dominant inflammation^{3,5}. Importantly, the repeated application of such compounds leads to responses different from those induced by a single challenge. Repeated treatment with antigenic compounds shifted the cytokine milieu from Th1 to Th2, resulting in increased infiltration of eosinophils and mast cells, and the induction of immediate- and late-phase responses^{3,6}. However, the molecular mechanisms responsible for the shift in the milieu are still unclear. Here we established a novel model of chronic allergic dermatitis in which antigen-nonspecific inflammation shifts the cytokine milieu to a Th2-dominant reaction¹¹. Namely, 12-*O*-tetradecanoyl 13-acetate (TPA) was painted twice on the ear lobes of PiCl-sensitized mice to induce antigen-nonspecific inflammation. The mice were then challenged with PiCl painted on the same ear lobe¹¹. This model showed features similar to

those observed in patients with atopic dermatitis: the formation of crust, epidermal hyperplasia and vigorous infiltration by leukocytes including eosinophils¹¹. The application of TPA induced a shift in the cytokine milieu from a Th1- to a Th2-type profile, resulting in an exacerbation of the PiCl-induced allergic dermatitis¹¹. Thus, this model would be suitable for studying the mechanisms by which antigen-nonspecific inflammation worsens allergic dermatitis.

Role of Thymic stromal lymphopoietin (TSLP) in the exacerbation of allergies

TSLP, an IL-7-like cytokine produced mainly by epithelial cells¹² and mast cells¹³, plays important roles in the initiation of allergic inflammation¹⁴. TSLP production is increased at inflamed sites in patients with severe asthma¹⁵, atopic dermatitis¹⁶, and allergic rhinitis¹⁷. The allergic inflammation in an animal model of asthma was significantly suppressed in TSLP receptor-deficient mice¹⁸. In addition, the intratracheal administration of anti-TSLP receptor significantly reduced infiltration of eosinophils, hyperplasia and Th2 cytokine production¹⁹. Lung-specific expression of TSLP induced asthma-like airway inflammation²⁰, and skin-selective expression and the intradermal injection of TSLP induced atopic dermatitis^{21,22}. Thus, an excess of TSLP is enough to cause allergic inflammation.

In our model, the application of TPA to the ear lobe of the PiCl-sensitized mice markedly increased the level of TSLP mRNA at 4 h¹¹. Thus TPA-induced production of TSLP might be one of the mechanisms responsible for the shift forward a Th2-dominant response.

Effects of chemicals in the environments on TSLP production and allergic dermatitis

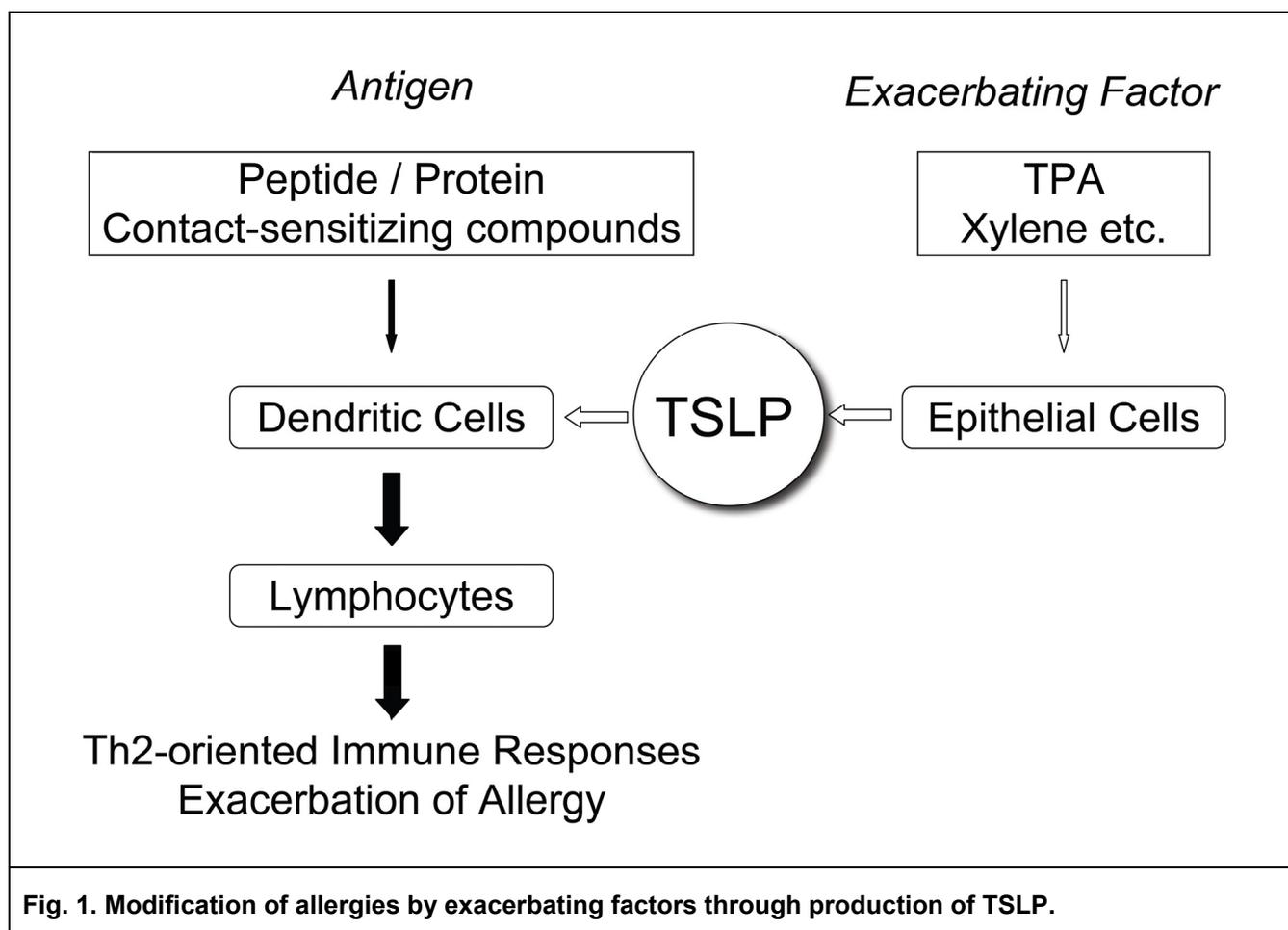
The first cells to interact with chemical compounds in the environment are the epithelial cells of the respiratory system, digestive tract and skin. Therefore, it is likely that chemicals which attach to epithelial tissues induce TSLP production by epithelial cells, promoting Th2-type reactions and worsening the allergic inflammation. Consequently, we assayed the activity of various chemical compounds, which are detected in the indoor environment, to induce TSLP production in ear lobes of mice. Among the organic solvents tested, xylene and related compounds such as 1,2,4-trimethylbenzene significantly induced the



production of TSLP protein. Interestingly, the activity to induce TSLP production was highly dependent on the position of methyl groups on the benzene ring. Namely, *m*-xylene induced much more extensively the production of TSLP than did *o*-xylene. These findings suggested that xylene triggered TSLP production by binding to a specific protein in a structure-dependent manner, and not through physical

and/or chemical toxicity.

When painted on the ear instead of TPA, xylene enhanced the PiCl-induced thickening of the ear and IL-4 production. Importantly, the xylene-induced enhancement of these responses was reversed in TSLP receptor-knockout mice, suggesting that xylene exacerbated the PiCl-induced allergic inflammation via production of TSLP.



Conclusion

Exogenous peptides/proteins and contact-sensitizing compounds act as antigens to induce allergies. However, the antigenicity of xylene itself has not been reported. Here we indicated that xylene, as well as TPA, exacerbated antigen-induced allergic inflammation via TSLP production (Fig. 1). Thus, there are chemicals in the environment which do not have contact-sensitizing activity but cause the production of TSLP and an exacerbation of allergic dermatitis. Our models would be useful to detect such compounds.

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