Mini Review

Expression of thymic stromal lymphopoietin (TSLP) in allergic rhinitis: Induction of tight junction proteins in human nasal epithelial cells and dendritic cells by epithelial-derived TSLP

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Thymic stromal lymphopoietin (TSLP) is an interleukin 7-like cytokine that triggers dendritic cell (DC)-mediated T helper 2-type inflammatory responses and is considered to be a master switch for allergic inflammation such as that in asthma and atopic dermatitis. Furthermore, proinflammatory cytokines and Toll-like receptor ligands can induce TSLP production in human bronchial epithelial cells and human keratinocytes. We first found high expression of endogenous TSLP in the epithelium of allergic rhinitis with recruitment and infiltration of DCs. In culture, the TSLP production in human nasal epithelial cells was markedly and significantly increased by treatment with the proinflammatory cytokines interleukin 1β /tumor necrosis factor-α and a Toll-like receptor 2 ligand, P_3CSK_4. Since it is also thought that TSLP expression not only activates DCs but also affects the epithelial barrier in allergic rhinitis, we investigated the effects of TSLP on tight junctions of human nasal epithelial cells and DCs *in vitro*. Treatment with TSLP enhanced the barrier function of human nasal epithelial cells *in vitro* together with an increase of the tight junction proteins claudin-1, -4,-7, and occludin. Furthermore, TSLP could exclusively induce claudin-7 expression in mouse DC line XS52, which expressed tight junction molecules claudin-1,-3,-4,-6,-7,-8, occludin and tricellulin.

These findings suggest that nasal epithelial-derived TSLP plays an important role in allergic rhinitis as well as asthma and atopic dermatitis and may control tight junctions of epithelial cells and DCs to preserve the epithelial barrier and promote direct sampling of antigens by DCs.

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Introduction

Allergic rhinitis is characterized by episodes of sneezing, rhinorrhea, nasal obstruction, and itching and results from a complex immunological cascade leading to dysregulated production of T helper 2 (Th2)-type cytokines such as interleukin 4 (IL-4), IL-5, and IL-13 as well as asthma and atopic dermatitis[1-3]. They trigger allergen-specific immunoglobulin E (IgE) production, eosinophilia, and mucus production[4-6]. However, the upstream events involving epithelial cells and antigen-presenting cells, particularly dendritic cells (DCs), and inducing the activation of the allergic immune cascade remain unknown in allergic rhinitis.

Epithelial cells are central participants in innate and adaptive immune responses as well as mucosal inflammation. These cells produce antimicrobial host defense molecules, proinflammatory cytokines and chemokines in response to activation via pathogen recognition receptors. Recruitment of immune cells, including DCs, T cells, and B cells into the proximity of epithelium results in the enhancement of adaptive immunity through interactions with epithelial cells. In particular, the epithelial barrier of the upper respiratory tract including the nasal cavity, which is the first site of exposure to inhaled antigens, plays an important role in host defense in terms of innate immunity and is regulated in large part by the apicalmost intercellular junctions, referred to as tight junctions[7,8]. The nasal epithelium may play an essential role in innate immunity to allergic rhinitis.

The tight junction, the apicalmost component of intercellular junctional complexes, separates the apical from the basolateral cell surface domains to establish cell polarity (performing the function of a fence). Tight junctions also possess a barrier function, inhibiting the flow of solutes and water through the paracellular space[9]. They are formed by integral membrane proteins such as occludin, claudin, junctional adhension molecules (JAMs), and tricellulin, as well as many peripheral membrane proteins, including zonula occludens 1 (ZO-1), ZO-2, ZO-3, MAGI-1, ASIP/PAR-3, PAR-6 and an atypical protein kinase C-interacting protein[10-13]. We previously reported that in the epithelium of human nasal mucosa from patients with allergic rhinitis, occludin, JAM-A, ZO-1, and claudin-1,-4,-7,-8,-12,-13 and -14 were detected together with well-developed tight junction strands[7].

DCs reside between epithelial cells in the gut, send dendrites outside the epithelium and directly sample bacteria[14]. However, the integrity of the epithelial barrier is preserved because DCs express tight junction proteins such as occludin, claudin-1, and ZO-1, and can establish tight junction-like structures with neighbouring epithelial cells[14].

DCs seem to play an important role in the pathogenesis of allergic rhinitis[15]. As in the gut epithelium, we previously also reported that HLA-DR- and CD11c-positive DCs expressed claudin-1 and penetrated beyond occludin in the epithelium of the nasal mucosa with, but not without, allergic rhinitis[7] (Fig.1). However, the mechanisms in the functional regulation of DCs in allergic rhinitis are still unclear.

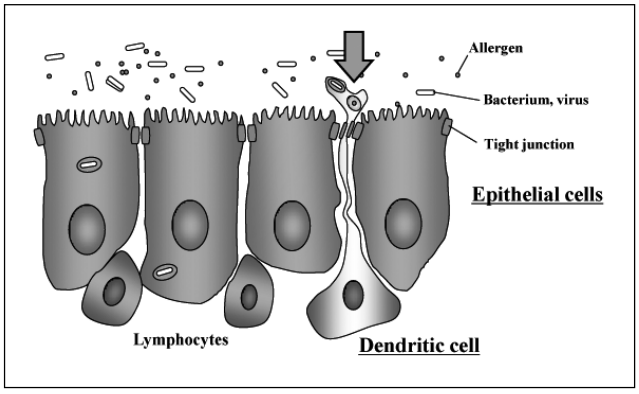

Fig.1 Diagram showing interaction between epithelial cells and DCs in nasal mucosa

Materials and Methods

1)Human tissue samples

Nasal mucosa tissues were obtained from 20 patients with allergic rhinitis (donors ranged in age from 12 to 65 years and had perennial rhinitis) and 20 patients without allergic rhinitis who were undergoing inferior turbinectomy at Sapporo Medical University, the Sapporo Hospital of Hokkaido Railway Company, or the KKR Sapporo Medical Center Tonan Hospital. The diagnosis of allergic rhinitis was established on the basis of the medical history and symptoms (sneezing, rhinorrhea and/or nasal congestion on most days) for at least 2 years, nasal cytology and specific IgE to aeroallergens (3.67-47.9 AU/ml IgE to house-dust allergens and 41.6-54.3 AU/ml IgE to mite allergens). Treatment with antihistamines and corticosteroids was stopped at least 4 weeks before the subjects entered the study. Informed consent was obtained from all patients, and this study was approved by the ethics committees of Sapporo Medical University, Sapporo Hospital of Hokkaido Railway Company, and KKR Sapporo Medical Center Tonan Hospital. Tissues were immediately frozen in liquid nitrogen and stored at -70℃ for immunohistochemistry and the extraction of RNA and protein.

2)Cell culture

The cultured human nasal epithelial cells (HNECs) that we used in this experiment were transfected with the catalytic component of telomerase, the human catalytic subunit of the telomerase reverse transcriptase (hTERT) gene, in primary cultured nasal epithelial cells derived from human nasal mucosa as described previously[16].

The cells were cultured in serum-free bronchial epithelial cell basal medium (BEBM) supplemented with bovine pituitary extract (1% v/v), 5 μg/ml insulin, 0.5 μg/ml hydrocortisone, 50 μg/ml gentamycin, 50 μg/ml amphotericin B, 0.1 ng/ml retinoic acid, 10 μg/ml transferrin, 6.5 μg/ml triiodothyronine, 0.5 μg/ml epinephrine, and 0.5 ng/ml epidermal growth factor (Lonza Walkersville, Inc.), 100 U/ml penicillin and 100 μg/ml streptomycin (Sigma-Aldrich). In this experiment, 2nd and 3rd passaged cells were used.

XS52 is DC line established from the epidermis of a newborn BALB/c mouse[17]. XS52 cells were incubated in RPMI-1640 medium (Sigma-Aldrich) supplemented with 10% fetal calf serum (Invitrogen), 10 mM HEPES, 1% non-essential amino acids, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, 0.25 μg/ml amphotericin B, $5x10^{-5}$ M 2-mercaptoethanol (Sigma-Aldrich), 1mM sodium pyruvate (Invitrogen), 2 ng/ml murine granulocyte/macrophage colony-stimulating factor (PeproTech EC), and the cultured supernatant (10% v/v) of the NS47 fibroblastic stromal cell line, which was cultured in modified RPMI-1640 medium[17].

3)Immunostaining

The frozen sections and the cells were fixed with cold acetone and ethanol (1:1) at -20℃ for 10 min. The specimens were incubated with monoclonal anti-leukocyte common antigen (LCA; clone PD7/26 and 2B11), anti-CD11c (clone KB90) (Dako A/S), polyclonal anti-thymic stromal lymphopoietin (TSLP; R&D Systems), and anti-claudin-7 (Zymed Laboratories) antibodies at room temperature for 1 h and then were incubated with Alexa 488 (green)- or Alexa 594 (red)-conjugated anti-sheep, anti-mouse, or anti-rabbit IgG (Molecular Probes Inc.) at room temperature for 1 h. Some sections were used for double staining of TSLP and LCA, TSLP and CD11c, and claudin-7 and CD11c. The specimens were examined and photographed with an Olympus IX 71 inverted microscope and confocal laser scanning microscope (MRC 1024; Bio-Rad). Phase-contrast photomicrographs were taken with a Zeiss Axiovert 200 inverted microscope.

4)RNA isolation and reverse transcription-polymerase chain reaction (RT-PCR) analysis

Total RNA was extracted and purified from human nasal mucosa and the cells using TRIzol reagent (Invitrogen) and reverse transcribed using oligo(dT)$_{12-18}$ primer and Superscript II reverse transcriptase (Invitrogen). PCR analysis was performed as described previously[7,16].

5)Western blotting analysis

Western blots of the human nasal mucosa and the cells were performed as described previously[16,18]. After electrophoretic transfer, the membranes were incubated with anti-TSLP (R&D Systems), anti-occludin, anti-claudin-1, anti-claudin-4, anti-claudin-7 (Zymed Laboratories), and anti-actin (Sigma-Aldrich) antibodies at room temperature for 1 h. The membrane was incubated with horseradish peroxidase-conjugated anti-sheep, anti-mouse, or anti-rabbit IgG (Dako A/S) at room temperature for 1 h. The immunoreactive bands were detected using an ECL Western blotting system (GE Healthcare UK).

6)Measurement of transepithelial electrical resistance (TER)

The cells were cultured to confluence on 12 mm Transwell, 0.4 μm pore-size filters (Corning Inc.) coated with rat tail collagen. TER was measured using an EVOM voltameter with an ENDOHM-12 (World Precision Instruments, Inc.) on a heating plate adjusted to 37℃. The values are expressed in standard units of ohms per square centimeter and presented as the mean ± SD.

7)Enzyme-linked immunosorbent assay (ELISA)

The concentration of the TSLP protein in cell-free supernatants of HNECs at 24 h after treatments was measured with a human TSLP ELISA kit (R&D Systems). The minimal detection limit for this kit was 31.25 pg/ml.

8)Data analysis

Signals were quantified using Scion Image Beta 4.02 Win (Scion Co.). Each set of results shown is representative of at least three separate experiments. Results are given as means ± SD. Differences between groups were tested by the two-tailed Student's *t* test for unpaired data.

Results and Discussion

1)TSLP and CD11c-positive DCs in the epithelium of allergic rhinitis

Epithelial-derived factor TSLP is an IL-7-like cytokine that potently induces deregulation of Th2 responses, a hallmark feature of allergic inflammatory diseases such as asthma and atopic dermatitis[19-21]. TSLP potently activates CD11c-positive DCs, and TSLP-stimulated DCs induce naïve $CD4^+$ T cells to differentiate into Th2 cells[20]. TSLP is produced by epithelial cells, skin keratino-cytes, stromal cells, smooth muscle cells, lung fibroblasts, and mast cells[20]. TSLP is highly expressed by crypt epithelial cells in the tonsils and sites of Th2 inflammation such as epidermal keratinocytes in the lesional skin of atopic dermatitis patients and asthmatic bronchial epithelium[20,21]. However, the role of TSLP in allergic rhinitis remains unknown.

We first found high expression of TSLP in the epithelium of

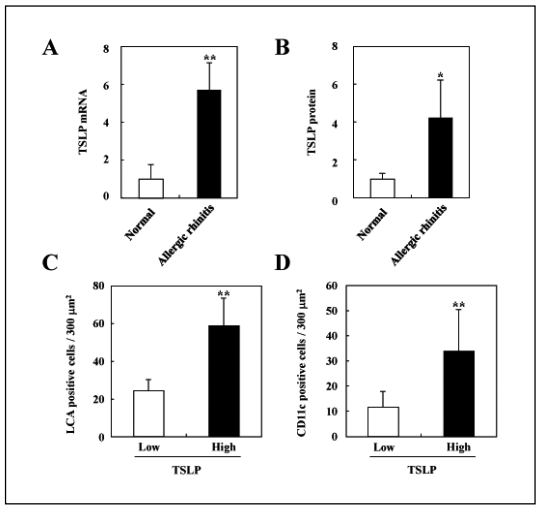

Fig.2 Expression of mRNA (A) and protein (B) of TSLP in nasal mucosa from controls and patients with allergic rhinitis. The numbers of LCA- and CD11c-positive cells (C,D) in nasal mucosa from patients with allergic rhinitis.

(A,B)** $p < 0.01$, * $p < 0.05$ versus normal. (C,D) ** $p < 0.01$ versus low.

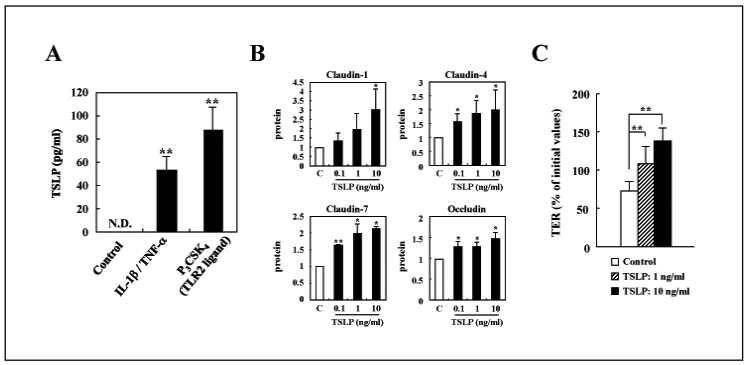

Fig.3 ELISA (A) of cultured HNEC-derived TSLP after treatment with IL-1 β/TNF- α or TLR2 ligand P_3CSK_4. Expression of tight junction proteins (B) and the barrier function measured as TER (C) in cultured HNECs after treatment with TSLP.

(A) N.D.: not detectable. ** $p < 0.01$ versus control. (B) C: control. ** $p < 0.01$, * $p < 0.05$ versus control. (C) n = 6. ** $p < 0.01$ versus control.

allergic rhinitis, compared to normal epithelium (Fig.2A,B). The numbers of LCA-positive cells and CD11c-positive DCs were significantly elevated in the nasal epithelium with high expression of TSLP compared to that with low expression of TSLP (Fig.2C,D). These findings indicate that epithelial-derived TSLP may play an important role in the development of allergic rhinitis as well as asthma and atopic dermatitis.

2) Induction of TSLP in human nasal epithelial cells (HNECs) *in vitro*

TSLP can be induced by the proinflammatory cytokines and Toll-like receptor (TLR) ligands in human bronchial epithelial cells and human keratinocytes[22-25]. In addition, in human bronchial epithelial cells, the mRNA for TSLP is significantly up-regulated by stimulation with IL-4 and IL-13, weakly up-regulated by tumor necrosis factor-α (TNF-α), transforming growth factor-β, and interferon-β, and both IL-1β and TNF-α are capable of inducing rapid TSLP production via NFκB in primary human bronchial epithelial cells[22,25]. Furthermore, the human TSLP mRNA levels are also increased after exposure to TLR2, TLR3, TLR8, and TLR9 ligands in human bronchial epithelial cells[22,25].

To investigate the mechanisms of the induction of TSLP in the epithelium of allergic rhinitis, HNECs were treated with cytokines (10 ng/ml IL-1β plus 10 ng/ml TNF-α) and a TLR2 ligand (1 μg/ml P_3CSK_4), and the production of TSLP was measured using ELISA. Treatment with IL-1β/TNF-α or P_3CSK_4 significantly induced TSLP production (IL-1β/TNF-α: 53 $\pm$ 12 pg/ml; P_3CSK_4: 87 $\pm$ 21 pg/ml), compared to the control (less than detection limit; 31.25 pg/ml) (Fig.3A). Furthermore, the mRNA and protein of TSLP were significantly increased in HNECs after treatment with IL-1β/TNF-α and P_3CSK_4 compared to the control (data not shown).

These findings suggested that the proinflammatory cytokines and TLR ligands which contributed to allergic rhinitis induced TSLP production in HNECs and also that the epithelial-derived TSLP might control DC function.

3) Induction of tight junction proteins in HNECs *in vitro* by TSLP

In allergic rhinitis, the detailed changes of barrier function remain unknown, although transepithelial migration of activated eosinophils induces a decrease of E-cadherin expression in cultured HNECs[26]. When we previously investigated the expression and function of tight junctions in the epithelium of allergic rhinitis, the protein expression, structures, and the barrier function of tight junctions were well maintained[7]. We hypothesized that TSLP expression not only activated DCs but also affected the maintenance of tight junctions in the epithelium of allergic rhinitis. Thus, we investigated the effects of TSLP on tight junctions of HNECs *in vitro*.

When HNECs were treated with 0.1-10 ng/ml TSLP for 24 h, protein expression of claudin-1,-4,-7, and occludin was increased from 0.1 ng/ml in a dose-dependent manner (Fig.3B). To investigate changes of the barrier function of tight junctions in HNECs after treatment with TSLP, TER was measured. The values of

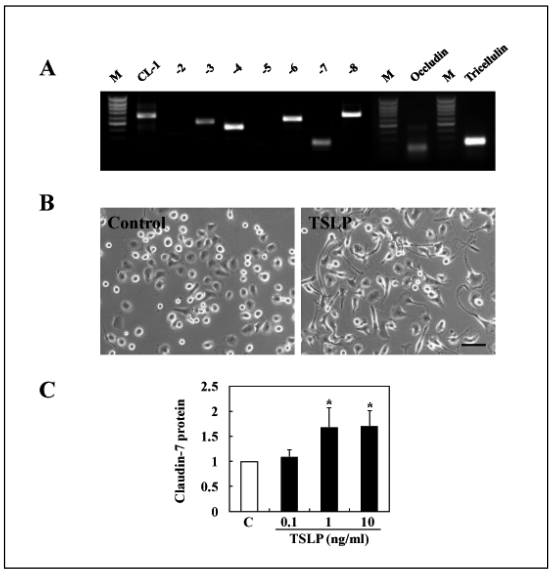

Fig.4 RT-PCR (A) for tight junction molecules in XS52 cells. Phase-contrast images (B, left: control, right: TSLP-treated) and expression of claudin-7 protein (C) in XS52 cells after treatment with TSLP.

(A) M: 100-bp ladder DNA marker. CL: claudin. (B) Bar: 40 μm. (C) C: control. * $p < 0.05$ versus control.

TER were significantly increased at 6 h after treatment with 1 and 10 ng/ml TSLP in a dose-dependent manner (Fig.3C). These findings suggested that the epithelial-derived TSLP might control the expression and function of tight junctions in the nasal epithelium in an autocrine manner.

4) Induction of tight junction proteins in DC line XS52 by TSLP

The epithelial DC population expresses high levels of the Langerhans cell (LC) marker Langerin and the tight junction proteins claudin-1, -7, and ZO-2[27]. Claudin-1 is detected in murine CD207$^+$ LCs residing in epidermis but not in other skin DCs and may have an important function in adhesion and migration of LC[28].

To investigate the regulation of tight junction proteins of DCs by TSLP, which is highly expressed in the epithelium of allergic rhinitis, we used mouse DC cell line XS52, which expresses CD11c, as a model of DCs in the nasal epithelium[17]. As shown in Figure 4A, mRNAs of claudin-1,-3,-4,-6,-7,-8, occludin and tricellulin were detected in XS52 cells. When the cells were treated with 10 ng/ml TSLP for 24 h, dendrites were elongated and the cells aggregated compared to the control (Fig.4B). In Western blotting, claudin-7 protein was significantly increased at more than concentration of 1 ng/ml TSLP (Fig.4C).

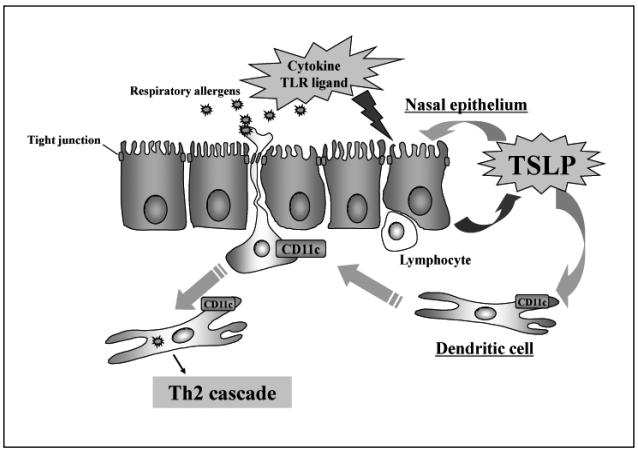

Fig.5 Diagram showing the roles of TSLP in allergic rhinitis

Conclusion

In some cases of allergic rhinitis, CD11c-positive DCs expressed claudin-7 and were colocalized at the cell borders facing the claudin-7-positive epithelium (data not shown). We therefore hypothesize as follows. Nasal epithelial-derived TSLP induced by stimuli such as cytokines and TLR ligands activates DCs and induces expression of integral tight junction proteins such as claudin-7 of DCs. On the other hand, the epithelial-derived TSLP also induces tight junction proteins, including claudin-7 of the nasal epithelium. Thus, the activated DCs may form tight junction-like structures with adjacent nasal epithelial cells and send dendrites outside through between the epithelial cells to directly sample respiratory allergens without a decrease in the barrier function (Fig.5). We think that TSLP is a master molecule for allergic rhinitis as well as asthma and atopic dermatitis.

Acknowledgments

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