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Effect of thymic stromal lymphopoietin on MUC5B expression in human airway epithelial cells

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) is an interleukin 7-like cytokine and a potent factor for B- and T-cell growth and differentiation. Recent studies have demonstrated an association of TSLP with allergic and inflammatory airway diseases. However, no study on the effect of TSLP on expression of mucin genes in airway epithelial cells has been reported. Therefore, the effects and brief signaling pathways of TSLP on expression of mucin genes in human airway epithelial cells were investigated in this study. In mucin-producing human NCI-H292 airway epithelial cells and primary cultures of normal nasal epithelial cells, the effect and signaling pathway of TSLP on expression of mucin genes were investigated using reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, enzyme immunoassay, and immunoblot analysis with several specific inhibitors and small interfering RNA (siRNA). In human NCI-H292 airway epithelial cells, TSLP increased MUC5B expression. TSLP significantly activated phosphorylation of ERK1/2 and p38 mitogen-activated protein kinase (MAPK). U0126 (ERK1/2 MAPK inhibitor) and SB203580 (p38 MAPK inhibitor) significantly attenuated TSLP-induced MUC5B mRNA expression. Knockdown of ERK1, ERK2, and p38 MAPK by ERK1, ERK2, and p38 MAPK siRNA significantly blocked TSLP-induced MUC5B mRNA expression. In the primary cultures of normal nasal epithelial cells, TSLP significantly increased MUC5B mRNA expression, which was significantly attenuated after pretreatment with U0126 and SB203580. These results suggest that TSLP induces MUC5B expression via the ERK1/2 and p38 MAPK signaling pathway in human airway epithelial cells.

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1. Introduction

In the human air way, mucus is a complex secretion which is mainly composed of water and ions, containing 2% mucin [1]. It provides an important function in protection of the airway from the external environment. Mucins, the glycoprotein component of mucus, impart physical and biological properties to mucus [2]. Overexpression of mucins leads to an increase in the morbidity and mortality of inflammatory respiratory diseases such as chronic bronchitis, chronic obstructive pulmonary disease (COPD) and asthma [3]. MUC4, MUC5AC, MUC5B, and MUC16, the predominant mucins in inflammatory airway disease, are regulated by many pathophysiological mediators and hormones, including bacterial proteinases and endotoxins, inflammatory mediators, and cytokines [3,4].

Thymic stromal lymphopoietin (TSLP), a novel interleukin (IL) 7-like cytokine, was first identified as a growth-promoting factor in cultured supernatants of a murine thymic stromal cell line [5,6]. TSLP is produced by several cell types, including human epithelial cells and stromal and muscular cells [7]. TSLP is a potent factor for B- and T-cell growth and differentiation, and has been implicated in the association with allergic airway inflammation, atopic dermatitis, inflammatory bowel diseases, and autoimmune disease [8]. Recent studies have demonstrated an association of TSLP with COPD as well as asthma [5,9,10]. However, no study on the effect of TSLP on expression of the mucin gene in human airway epithelial cells has been reported. Therefore, the goal of this study was to determine whether TSLP might play an important role in regulation of secretion of major mucins in airway epithelial cells. In this study, the effects and brief signaling pathways of TSLP on MUC4, MUC5AC, MUC5B, and MUC5B expression in human airway epithelial cells were investigated.

2. Materials and methods

2.1. Materials

TSLP (1398-TS) was obtained from R&D Systems (Wiesbaden-Nordenstadt, Germany). Mucin-producing human NCI-H292

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airway epithelial cells were obtained from the American Type Culture Collection (Manassas, VA, USA). RPMI 1640 medium and Trizol were obtained from Invitrogen (Carlsbad, CA, USA). EpiLife medium and human keratinocyte growth supplement were obtained from Cascade Biologics (Portland, OR, USA). Reverse transcriptase-polymerase chain reaction (RT-PCR) kits were obtained from Applied Biosystems (Foster City, CA, USA). Real-time PCR kits were obtained from Roche Applied Science (Mannheim, Germany). Fetal bovine serum (FBS) was obtained from Hyclone Laboratories (Logan, UT, USA). Enhanced chemiluminescence reagents were obtained from Perkin Elmer Life Sciences (Boston, MA, USA). Anti-goat horseradish peroxidase (HRP)-conjugated primary antibody (sc-23024) and secondary antibody (sc-2020) of MUC5B were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Extracellular signal related kinase (ERK) 1/2, phospho-ERK1/2, p38 and phospho-p38 were purchased from Cell Signaling Technology (Danvers, MA, USA). The specific inhibitors, U0126 and SB203580, were purchased from Calbiochem (San Diego, CA, USA) and BIOMOL (Plymouth Meeting, PA, USA), respectively. OPTI-MEM I Reduced Serum Medium, Lipofectamine 2000, and predesigned small interfering RNA (siRNA) targeting control, ERK1 mitogen-activated protein kinase (MAPK), ERK2 MAPK, and p38 MAPK were purchased from Invitrogen Corporation (Carlsbad, CA, USA).

For the primary culture, nasal mucosa was obtained from normal inferior turbinate samples from 10 patients undergoing augmentation rhinoplasty who had no personal or family history of allergy, and who had negative results on skin-prick tests to 20 common airborne allergens and on multiple simultaneous allergen tests. This study was approved by the institutional review board for human studies at Yeungnam University Medical Center and written informed consent was obtained from each patient.

2.2. Cell culture and treatment

Human NCI-H292 airway epithelial cells were cultured in RPMI 1640 medium supplemented with 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% FBS. The cells were grown at 37 °C in 5% CO_2 fully humidified air and subcultured twice weekly. When the cultures were confluent, the cells were incubated in RPMI 1640 medium containing 0.5% FBS for 24 h. The cells were then rinsed with serum-free RPMI 1640 medium and exposed to the indicated concentrations of TSLP.

For the primary culture of human nasal epithelial cells, the nasal mucosal tissue was washed with phosphate-buffered saline (PBS) and immersed in dispase (Boehringer Mannheim Biochemica, Mannheim, Germany) for 90 min. After the tissue was scraped off the surface of the nasal mucosa using a scalpel, it was added to 1% PBS and filtered through a mesh. The cells were seeded in a 24-well plate at 2.5×10^5 cells/well and were then incubated with EpiLife medium and human keratinocyte growth supplement (5 mL/500 mL of medium). When the cultures were confluent, the cells were exposed to the indicated concentrations of TSLP.

To investigate the brief signaling pathway of mucin gene expression, human NCI-H292 airway epithelial cells and human nasal epithelial cells were pretreated with U0126 or SB203580 for 1 h before exposure to TSLP. For the controls, human NCI-H292 airway epithelial cells and human nasal epithelial cells were incubated with the medium alone for the same amount of time.

2.3. RT-PCR of MUC16, MUC5B, MUC5AC, and MUC4 mRNA expression

Total RNA was isolated from human NCI-H292 airway epithelial cells according to the manufacturer's instructions (Applied Biosystems). Each sample was reverse transcribed into cDNA using the GeneAmp RNA PCR Core Kit. PCR for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was performed on each individual sample as a positive control. The primer sequences and conditions used were according to previously published protocols for MUC16, MUC5B, MUC5AC, and MUC4 [11,12]. PCR products were electrophoresed on a 2% agarose gel, stained with ethidium bromide, and visualized by ultraviolet fluorescence. Semiquantitative analysis of the RT-PCR product was performed on the scanned gel images, and the intensity of the PCR product was measured using commercially available imaging software (Scion, Frederick, MD, USA). The relative intensity of individual bands on the gel image was determined as the ratio of intensities of MUC5B to the intensity of GAPDH.

2.4. Real-time PCR analysis of MUC5B mRNA

Real-time PCR was performed using the LC Fast Start DNA Master SYBR Green kit using 0.5 μL of cDNA, corresponding to 25 ng of total RNA at a final volume 10 μL, 2.5 mM $MgCl_2$, and 0.5 μM of each primer (final concentration). Quantitative PCR was performed using a LightCycler for 45 cycles at 95 °C for 10 s, specific annealing temperature for 5 s and 72 °C for 10 s. Data were normalized to GAPDH. Amplification specificity was evaluated using melting curve, following the manufacturer's instructions (Roche Applied Science).

2.5. Immunoassay for MUC5B protein

Human NCI-H292 airway epithelial cells were prepared and treated with TSLP as described above. Following 24 h of TSLP incubation, MUC5B protein level was determined using an enzyme-linked immunosorbent assay (ELISA). Each sample of cell lysate or supernatant from NCI-H292 cells was incubated at 40 °C in a 96-well plate until dry. Plates were blocked with 2% bovine serum albumin and incubated with primary antibody with PBS containing 0.05% Tween 20 for 1 h. Wells were treated with dispensation of HRP-conjugated secondary antibody into each well. After 4 h, color was developed using 3,3′,5,5′-tetramethylbenzidine peroxidase solution and stopped with 2 N-H_2SO_4. Optical density measurements were obtained using an EL800 ELISA reader (BIO-TEK Instruments, Winooski, VT, USA) at 450 nm. The results were expressed as percent of baseline control.

2.6. Western blot analysis of ERK1/2 and p38 MAPK

Human NCI-H292 airway epithelial cells were seeded in each well of a 6-well plate and treated with TSLP. The cells were exposed to trypsin, and formed into pellets at 700 g at 4 °C and pellets were resuspended in lysis buffer (50 mM Tris–HCl, pH 8.0, 5 mM EDTA, 150 mM NaCl, 1% Triton X-100, 1 mM phenylmethylsulfonyl fluoride, and protease inhibitor cocktail). The preparation was then clarified by centrifugation, and the supernatant was saved as a whole-cell lysate. Proteins (20 μg) were separated using 10% reducing sodium dodecyl sulfate–polyacrylamide gel electrophoresis and electroblotted in 20% methanol, 25 mM Tris, and 192 mM glycine onto a nitrocellulose membrane. The membrane was blocked with 5% nonfat dry milk in 25 mM Tris–HCl, 150 mM NaCl, and 0.2% Tween 20, followed by incubation with the indicated primary antibody of ERK1/2 or p38 for 4 h. Subsequently, the membrane was incubated for 1 h with secondary antibody of ERK1/2 or p38 conjugated to HRP, and developed using an enhanced chemiluminescence system kit. Bands were detected after exposure to X-ray film for 10 s.

2.7. Cell transfection with siRNA for ERK1, ERK2, and p38 MAPK

To verify involvement of ERK1/2 and p38 MAPK in TSLP-induced MUC5B expression, human NCI-H292 airway epithelial cells were transfected with control, ERK1, ERK2, and p38 MAPK siRNA. The sequences and conditions used were according to previously published protocols for control, ERK1, ERK2, and p38 siRNA [13]. Transfection was performed according to the manufacturer's protocol (Invitrogen Corporation, Carlsbad, CA, USA). In brief, human NCI-H292 airway epithelial cells were seeded in a 6-well plate at 1×10^5 cells/well and incubated overnight in RPMI 1640 medium without antibiotics. When the cells were 80–90% confluent, the following day, the cells were washed with PBS; OPTI-MEN I Reduced Serum Medium (Invitrogen Corporation, Carlsbad, CA, USA) was then added to the cells. ERK1 MAPK siRNA and a nucleic acid transferring agent, Lipofectamine 2000 (Invitrogen Corporation, Carlsbad, CA, USA), were incubated together in OPTI-MEM I Reduced Serum Medium for 20 min at room temperature to form an ERK1 MAPK siRNA-Lipofectamine complex. The ERK1 MAPK siRNA-Lipofectamine complex-containing medium was added to each well containing the cells to a final ERK1 MAPK siRNA concentration of 20 nM and the cells were then incubated for 24 h at 37 °C in a CO_2 incubator. The ERK1 MAPK siRNA-Lipofectamine complex-containing medium was replaced with RPMI 1640 medium after 4 h without loss of transfection activity. After 24 h of transfection with ERK1 MAPK siRNA, the cells were exposed to the indicated concentrations of TSLP and then harvested for RT-PCR analysis of MUC5B mRNA expression. The transfection rate of ERK1 MAPK siRNA was verified to be over 90% in human NCI-H292 airway epithelial cells. The same procedure was performed with control, ERK2 MAPK, and p38 MAPK siRNA.

2.8. Statistical analysis

Statistical analysis was performed using SPSS, version 12.0 (SPSS, Chicago, IL, USA). The mean for each of the obtained quantitative values was calculated. Comparisons were made using the Student's *t*-test. For all tests, p value < 0.05 was considered statistically significant.

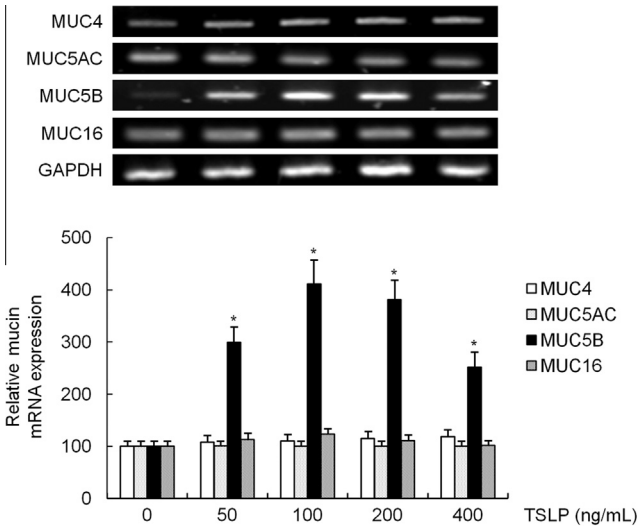

Fig. 1. The effect of TSLP on MUC4, MUC5AC, MUC5B, and MUC16 expression in human NCI-H292 airway epithelial cells. Results of RT-PCR showed that TSLP significantly induced MUC5B mRNA expression. However, TSLP did not induce MUC4, MUC5AC, and MUC16 mRNA expression. Images are representative of three separate experiments performed in triplicate. Bars indicate the average ± S.D. of three independent experiments performed in triplicate. *p < 0.05 compared with zero value.

3. Results

3.1. TSLP induced MUC5B expression in human NCI-H292 airway epithelial cells

To investigate the effect of TSLP on MUC4, MUC5AC, MUC5B, and MUC16 expression in human NCI-H292 airway epithelial cells, the cells were incubated with different doses of TSLP for 8 h. Results of RT-PCR showed that TSLP significantly induced MUC5B mRNA expression. However, TSLP did not induce MUC4, MUC5AC, and MUC16 mRNA expression (Fig. 1).

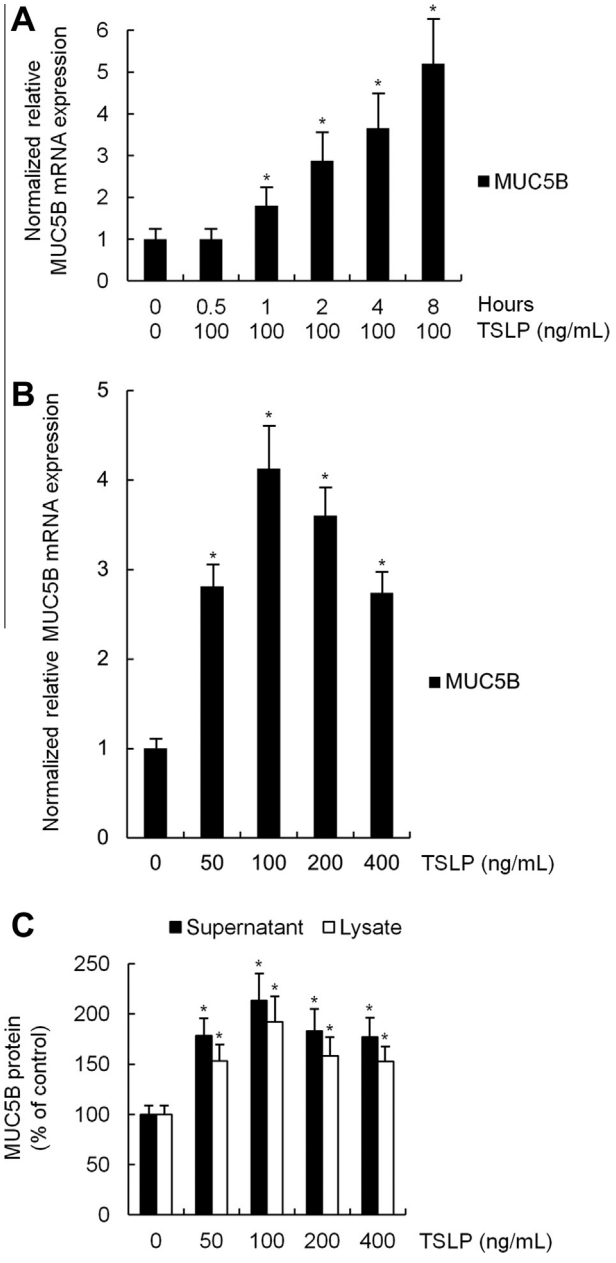

Fig. 2. The effect of TSLP on MUC5B expression in human NCI-H292 airway epithelial cells. (A) Results of real-time PCR showed that MUC5B mRNA expression was significantly increased at all times, and peaked at 8 h after exposure to TSLP (100 ng/mL). (B and C) Results of real-time PCR and ELISA showed that MUC5B expression was significantly increased at all concentrations of TSLP, and peaked at 100 ng/mL of TSLP. Images are representative of three separate experiments performed in triplicate. Bars indicate the average ± S.D. of three independent experiments performed in triplicate. *p < 0.05 compared with zero value.

To investigate the effect of TSLP on MUC5B expression with dose- and time-dependent experiments, NCI-H292 airway epithelial cells were treated with different doses of TSLP for 8 h or TSLP (100 ng/mL) for variable times. Results of real-time PCR showed that MUC5B mRNA expression was significantly increased at all times, and peaked at 8 h after exposure to TSLP (100 ng/mL) (Fig. 2A): TSLP induced MUC5B mRNA expression in a time-dependent manner. Results of real-time PCR and ELISA showed that MUC5B expression was significantly increased at all concentrations of TSLP, and peaked at 100 ng/mL of TSLP (Fig. 2B and C): however, TSLP did not induce MUC5B expression in a dose-dependent manner.

3.2. ERK1/2 and p38 MAPK were involved in TSLP-induced MUC5B expression in human NCI-H292 airway epithelial cells

To investigate the signaling pathways involved in TSLP-induced MUC5B expression, human NCI-H292 airway epithelial cells were stimulated with TSLP (100 ng/mL) and then Western blot was performed for analysis of phosphorylation of ERK1/2 and p38 MAPK. With the passage of time, phosphorylation of ERK1/2 and p38 MAPK were significantly increased (Fig. 3A): phosphorylation of ERK1/2 MAPK was stronger than phosphorylation of p38 MAPK. In addition, the cells were incubated with TSLP (100 ng/mL) for 8 h after pretreatment with specific inhibitors for ERK1/2 MAPK (U0126) and p38 MAPK (SB203580) for 1 h. Results of RT-PCR and ELISA showed that TSLP-induced MUC5B expression was significantly attenuated by pretreatment with U0126 and SB203580 (Fig. 3B and C). To confirm this signaling pathway, the cells were transfected with ERK1, ERK2, and p38 MAPK siRNA. The cells were then exposed to TSLP (100 ng/mL). Results of RT-PCR showed that the knockdown of ERK1, ERK2, and p38 MAPK by ERK1, ERK2, and p38 MAPK siRNA significantly blocked TSLP-induced MUC5B mRNA expression (Fig. 3D): the knock down ratio was verified to be over 75%.

3.3. Effect of TSLP on MUC5B expression in human nasal epithelial cells

RT-PCR analysis was used in investigation of the effect of TSLP in primary cultures of normal nasal epithelial cells. MUC5B mRNA expression was significantly increased by treatment with TSLP (100 ng/mL). TSLP-induced MUC5B mRNA expression was significantly attenuated by pretreatment with U0126 (ERK1/2 MAPK inhibitor) and SB203580 (p38 MAPK inhibitor) (Fig. 4).

4. Discussion

The human TSLP gene is located on chromosome 5q22.1, next to the atopic cytokine cluster on 5q31 [5]. TSLP is a four-helix bundle

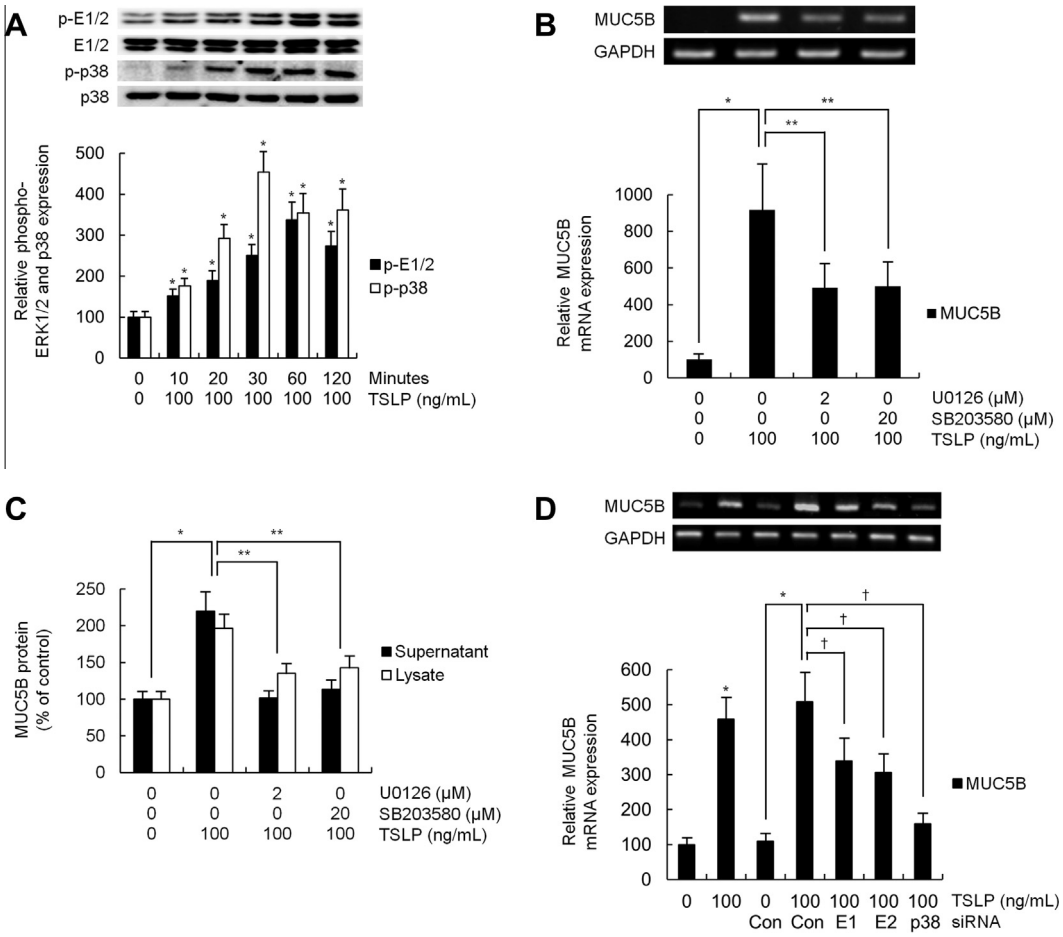

Fig. 3. Phosphorylation of ERK1/2 and p38 MAPK of TSLP-induced MUC5B expression in human NCI-H292 airway epithelial cells. (A) Results of Western blot showed that TSLP significantly activated the phosphorylation of ERK1/2 and p38 MAPK. (B and C) Results of RT-PCR and ELISA showed that TSLP-induced MUC5B expression was significantly attenuated by pretreatment with U0126 (ERK1/2 MAPK inhibitor) and SB203580 (p38 MAPK inhibitor). (D) Results of RT-PCR showed that the knockdown of ERK1, ERK2, and p38 MAPK by ERK1, ERK2, and p38 MAPK siRNA significantly blocked TSLP-induced MUC5B mRNA expression. Images are representative of three separate experiments performed in triplicate. Bars indicate the average ± S.D. of three independent experiments performed in triplicate. E1, extracellular regulated kinase 1; E2, extracellular regulated kinase 2; p-E1/2, phosphorylated extracellular regulated kinase 1/2; p-p38, phosphorylated p38; Con, control. $^{*}p < 0.05$ compared with zero value. $^{**}p < 0.05$ compared with TSLP (100 ng/mL) alone. $^{\dagger}p < 0.05$ compared with TSLP (100 ng/mL) and control siRNA.

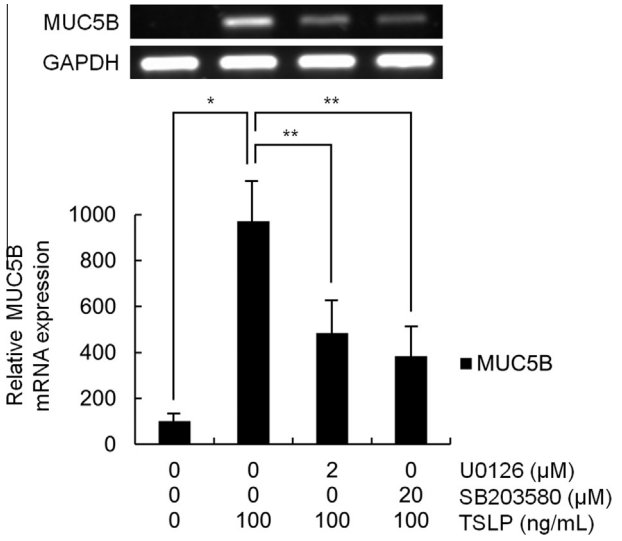

Fig. 4. The effect of TSLP on MUC5B expression in human nasal epithelial cells. Results of RT-PCR showed that MUC5B mRNA expression was significantly increased by treatment with TSLP (100 ng/mL). TSLP-induced MUC5B mRNA expression was significantly attenuated by pretreatment with U0126 (ERK1/2 MAPK inhibitor) and SB203580 (p38 MAPK inhibitor). Images are representative of three separate experiments performed in triplicate. Bars indicate the average ± S.D. of three independent experiments performed in triplicate. $^{*}p < 0.05$ compared with zero value. $^{**}p < 0.05$ compared with TSLP (100 ng/mL) alone.

cytokine, which presents a structural and functional homology to IL-7, and binds TSLP receptor consisting of the IL-7 receptor α-chain and a common γ receptor-like chain [7,14]. TSLP is normally expressed by epithelial cells, skin keratinocytes, stromal cells, smooth muscle cells, fibroblasts of lung, and mast cells [9]. The biological role of TSLP is a potent factor for driving T helper (Th) 2-mediated inflammation; TSLP activates dendritic cells, which induce Th2 cell differentiation during the induction phase of the immune response. TSLP also directly promotes T-cell proliferation through T-cell receptor activation, and supports B-cell differentiation. In addition, TSLP amplifies Th2 cytokine production by mast cells and natural killer T cells [8]. Expression of TSLP is regulated by several factors, including trauma, mechanical injury, infection with microbes, Toll-like receptor ligand, and host-derived pro-inflammatory and Th2 cytokines [5,8,15]. Several recent studies have reported that TSLP is over-expressed in inflammatory airway disease, such as nasal polyp, asthma, and COPD, suggesting that TSLP may play an important role in the pathogenesis of nasal polyp, asthma, and COPD [5,6,9,14,15]. However, no study on the effect of TSLP on expression of the mucin genes in human airway epithelial cells has been reported. Therefore, this study focused on the relationship between TSLP and mucin genes in human NCI-H292 airway epithelial cells and primary cultures of normal nasal epithelial cells. Findings of this study showed that TSLP only induced MUC5B expression, compared with MUC4, MUC5AC, and MUC16 expression.

Regarding the signaling pathway about TSLP, TSLP induces chemotactic and prosurvival effects in eosinophils through the activation ERK and p38 MAPK signaling pathway [16], and TSLP is associated with chemokines expression in human airway smooth muscle cells via ERK and p38 MAPK signaling pathway [17]. As to the signaling pathway of MUC5B expression, MUC5B expression is induced in response to a wide variety of stimuli, including nerve activation and inflammatory cytokines such as IL-1β, IL-6, IL-9, IL-13, or tumor necrosis factor-α via the ERK1 and p38 MAPK signaling pathway in human airway epithelial cells [13,18]. Therefore, this study focused on TSLP-induced MUC5B expression via the ERK1 and p38 MAPK signaling pathway. The results of this study showed that TSLP significantly activated phosphorylation of ERK1/2 and p38 MAPK. ERK1/2 MAPK inhibitor and p38 MAPK inhibitor significantly attenuated TSLP-induced MUC5B expression. In addition, knockdown of ERK1, ERK2, and p38 MAPK by ERK1, ERK2, and p38 MAPK siRNA significantly blocked TSLP-induced MUC5 expression. These results suggest that TSLP increased MUC5B expression via the ERK1/2 and p38 MAPK signaling pathway as with IL-1β, IL-6, IL-9, IL-13, or tumor necrosis factor-α.

In conclusion, the results of this study demonstrate for the first time that TSLP-induced MUC5B expression via the ERK1/2 and p38 MAPK signaling pathway in human airway epithelial cells. Although the effects of TSLP on mucins and the precise signaling pathways of TSLP on mucin genes in airway epithelial cells remain to be determined, these results provide important information indicating that TSLP may play a role in regulation of mucus-secretion through MAPK signaling pathways in human airway epithelial cells.

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