Platelet-derived growth factor mediates interleukin-13-induced collagen I production in mouse airway fibroblasts

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Interleukin-13 (IL-13) is associated with the production of collagen in airway remodelling of asthma. Yet, the molecular mechanisms underlying IL-13 induction of collagen remain unclear; the aim of this study is to address this issue. IL-13 dose- and time-dependently-induced collagen I production in primary cultured airway fibroblasts; this was accompanied with the STAT6 phosphorylation, and pre-treatment of cells with JAK inhibitor suppressed IL-13-induced collagen I production. Further study indicated that IL-13 stimulated JAK/STAT6-dependent PDGF production and subsequent ERK1/2 MAPK activation in airway fibroblasts, and the presence of either PDGF receptor blocker or MEK inhibitor partially suppressed IL-13-induced collagen I production. Taken together, our study suggests that activation of JAK/STAT6 signal pathway and subsequent PDGF generation and resultant ERK1/2 MAPK activation mediated IL-13-induced collagen I production in airway fibroblasts.

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1. Introduction

Airway remodelling is one of the characteristic features of asthma and is defined as changes in composition, content and organization of cellular and molecular constituents of airway (Yang *et al.* 2004; Zhang and Li 2011). Overproduction and deposition of extracellular matrix (ECM), particularly collagen I in the sub-epithelium, is the most notable pathologic alters of airway remodelling, although the molecular mechanisms are still unclear (Halwani *et al.* 2010, 2011). Therefore, exploring the molecular mechanisms underlying the increase of collagen and searching for appropriate intervention are important in the management of asthma.

Interleukin-13 (IL-13) is a major T helper 2 (Th2) cytokine produced mainly by the activated T cells and plays a crucial role in pathogenesis of airway inflammation and remodelling in asthma (Yang *et al.* 2004). Firszt *et al.* have shown that IL-13 stimulates airway fibroblasts isolated from patients with asthma to produce collagen I (Firszt *et al.* 2014). The detailed molecular mechanisms underlying the effect of IL-13 on collagen I production remain largely unclear. Studies have shown that IL-13 induces the production of platelet-derived growth factor-AA (PDGF-AA) in rat lung fibroblasts by activation of JAK/STAT6 signal pathway (Ingram *et al.* 2004). As an important stimulator of fibrosis, PDGF has been widely associated with fibrotic diseases including idiopathic pulmonary fibrosis (IPF) (Bonner 2004; Abdollahi *et al.* 2005). However, it is unknown whether IL-13 stimulates PDGF production in airway fibroblasts, or whether the induction of PDGF is associated with the generation of collagen I and which signalling cascades are activated to mediate this effect.

To address issues mentioned above, primary cultured mouse airway fibroblasts were stimulated with IL-13, and collagen I production and phosphorylation of STAT6 were determined. We further examined whether induction of

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PDGF contributed to IL-13-induced collagen production, and its mechanisms were also explored.

2. Materials and methods

2.1 *Cell preparation and culture*

Primary airway fibroblasts were obtained from the bronchia of Balb/c mice (15–20 g) using the method reported by Lindemann and Racké (2003). Briefly, the isolated bronchia was incised longitudinally and the epithelium and smooth muscle layer were rubbed off with a moistened cotton stick and a surgical blade. The remaining thin adventitia layer was cut into small pieces (about 2 mm^2) and then placed into 10 cm Petri dishes in Dulbecco's modified Eagle's medium (DMEM)/High glucose (Invitrogen, USA) with 15% (v/v) fetal bovine serum (FBS; Sigma-Aldrich, USA), 100 U/mL penicillin (10 µL penicillin stock solution was added), 100 µg/mL streptomycin (10 µL streptomycin stock solution was added), and cultured at 37°C in a humidified, 5% (v/v) CO2 incubator. Cells were passaged by trypsinization using 0.25% (w/v) trypsin (Invitrogen). Cells between passages 4 and 8 were used for the experiments described below. The purity of fibroblasts was determined by immunostaining against vimentin (Sigma-Aldrich, USA) and α-smooth muscle actin (α-SMA; Sigma-Aldrich, USA). Fluorescence microscope images indicate that cells contained more than 95% of fibroblasts (positive for vimentin and negtative for α-SMA; data not shown here). Fibroblasts were incubated in 1% (v/v) FBS-DMEM for 12 h to minimize the serum-induced effects before each experiment. IL-13 (Peprotech, USA) was dissolved in ddH20 at 100 µg/mL as the stock solution. A77 1726 (BioVision, USA), PD98 059 (Alexis Biochemicals, USA) and trapidil (Enzo Life Science, France) were dissolved in 100% dimethyl sulfoxide (DMSO) at 100 mM as stock solution and were used to inhibit JAK, MEK and PDGF receptor, respectively. The same volume of 100% DSMO was added to control samples in the experiments.

2.2 *Measurement of PDGF-AA*

PDGF-AA level was measured in conditioned medium using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA). Assays were performed following the established protocol (Bosse *et al.* 2008). Each sample was run in duplicate. The concentration of each sample was calculated automatically by the instrument software according to the measured optical density values.

2.3 *Collagen I assay*

Collagen I was determined in conditioned medium using commercially available ELISA assay kit (MyBioSource, USA) according to the established protocol (Howard *et al.* 2014).

2.4 *Immunoblotting*

Cells were lysed in lysis buffer containing 50 mM Tris-HCl (pH 7.4), 1% NP-40, 0.1% SDS, 150 mM NaCl, 0.5% sodium-deoxycholate, 1 mM EDTA, 1 mM PMSF, 1 mM Na3VO4, 1 mM NaF and proteinase inhibitors. The supernatant of cell lysis was obtained by centrifugation at 14,000 rpm for 15 min at 4°C, and protein concentration was measured with a bicinchoninic acid assay (BCA; Pierce, USA) kit. Protein was resolved on a SDS-PAGE gel and transferred to a nitrocellulose (NC; Bio-Rad, USA) membrane via semidry transfer. The NC membrane was then blocked with 5% (w/v) nonfat dry milk in phosphate buffered saline (PBS) containing 0.1% (v/v) Tween-20. Polyclonal or monoclonal antibodies were used to against phosphor-STAT6 (p-STAT6; Abcam Inc, USA), total-STAT6 (t-STAT6; Cell Signaling Technology, USA), phosphor-ERK1/2 (p-ERK1/2; Cell Signaling Technology, USA) and total-ERK1/2 (t-ERK1/2; Cell Signaling Technology, USA) according to the established protocols (Krejci *et al.* 2009, Tognon *et al.* 2001). Horseradish peroxidase (HRP)-conjugated goat anti-mouse or anti-rabbit IgG was used as the secondary antibodies (Sigma-Aldrich, USA). Reactions were visualized by the enhanced chemiluminescence (Pierce, USA) and then were exposed to the autoradiographic film. Bands were quantified by scanning films with the Scion Image software. Band quantification of aimed proteins was standardized by GAPDH or related total protein.

2.5 *Statistics*

All values are presented as mean ± standard deviation (S.D.). Data were analysed using one-way analysis of variance (ANOVA) followed by Tukey *post hoc* tests. Probability values of $p<0.05$ were considered to represent a statistically significant between groups.

3. Results

3.1 *Effect of IL-13 on collagen I production in primary cultured mouse airway fibroblasts*

To determine whether IL-13 stimulates collagen I production in airway fibroblasts to contribute to airway remodelling, primary cultured airway fibroblasts were stimulated with

different concentrations of IL-13 for different times, and the level of collagen I in conditioned medium was measured using ELISA. As shown in figure 1A, IL-13 time-dependently induced collagen I production; peak time for 100 ng/mL IL-13 (one thousand dilution from stock solution) induction of collagen I production was 48 h. Figure 1B indicates that IL-13 triggered collagen I expression in a dose-dependent manner; 100 ng/mL IL-13 caused a 2.43-fold increase in collagen I production (p <0.01 versus control), suggesting that IL-13 increased collagen I expression in airway fibroblasts.

3.2 *Activation of JAK/STAT6 signalling mediates IL-13-triggered collagen I production in primary cultured mouse airway fibroblasts*

To address the molecular mechanisms underlying IL-13 induction of collagen I production in airway fibroblasts, airway fibroblasts were stimulated with different concentrations of IL-13 for different times; phosphorylation of STAT6 was examined using Western blot. As shown in figure 2A, IL-13 time-dependently increased phosphorylation level of STAT6; peak time for 100 ng/mL IL-13 induction of STAT6 phosphorylation was 15 min. Figure 2B indicates that IL-13 dose-dependently-induced phosphorylation of STAT6 at 15 min; 100 ng/mL IL-13 caused a 2.84-fold increase in STAT6 phosphorylation compared with control (p <0.01).

To investigate the involvement of JAK/STAT6 signal pathway in IL-13-induced collagen I production, primary cultured airway fibroblasts were pretreated with JAK inhibitor A77 1726 (50 μM) for 1 h before stimulation of cells with 100 ng/mL IL-13 for 48 h. Figure 2C shows that inhibition of JAK significantly reduced IL-13-induced collagen I production (p <0.01), indicating that JAK/STAT6 signal pathway particularly mediated IL-13-induced collagen I generation.

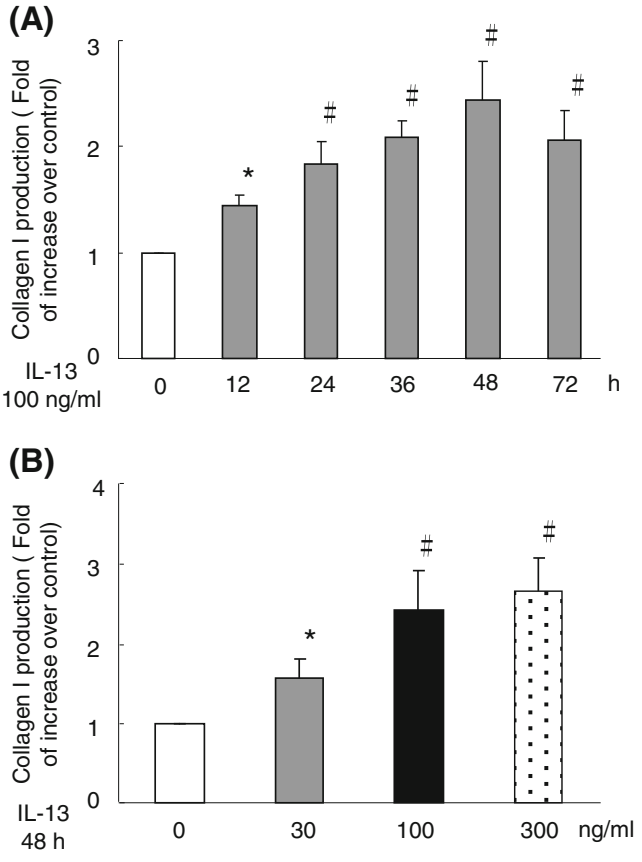


Figure 1. IL-13 induces collagen I production in mouse airway fibroblasts. (**A**) Primary cultured mouse airway fibroblasts were stimulated with 100 ng/mL IL-13 at different time points. Collagen I was determined in conditioned medium using ELISA (n=4 each group). (**B**) Cells were treated with different concentrations of IL-13 for 48 h, and the level of collagen I was measured using ELISA (n=4 each group).*p<0.05, #p<0.01 versus control cells (Con).

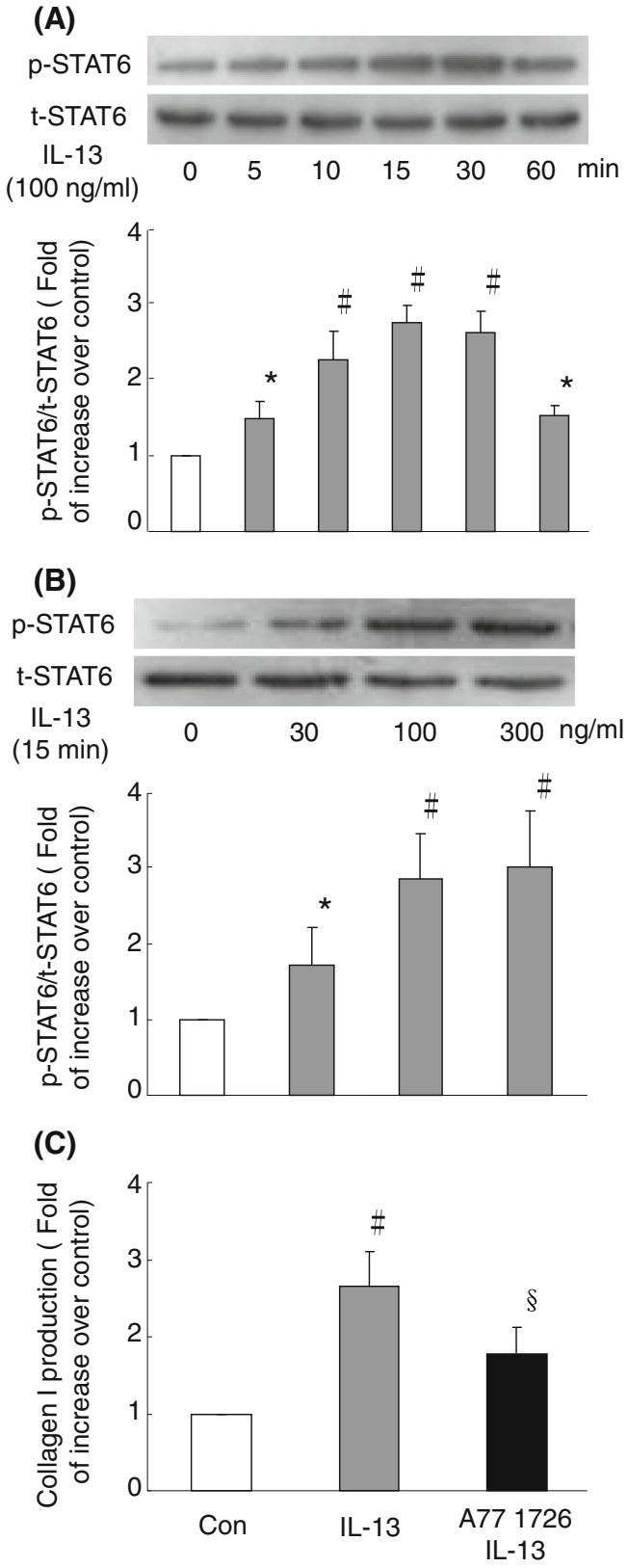
3.3 *Effect of IL-13 on PDGF production in primary cultured mouse airway fibroblasts*

It has been shown that IL-13 up-regulates PDGF expression in lung fibroblasts (Ingram *et al.* 2004), and to determine whether IL-13 also stimulates PDGF production in airway fibroblasts to associate with airway remodelling in asthma, primary cultured mouse airway fibroblasts were exposed to different concentrations of IL-13 at different time points; the level of PDGF-AA was examined in conditioned medium using ELISA. Figure 3A and 3B indicate that IL-13 time- and dose-dependently increased level of PDGF-AA; peak time for 100 ng/ml IL-13 induction of PDGF-AA was 24 h, and 2.6-fold increase of PDGF-AA was achieved with 100 ng/mL IL-13 at 24 h compared with control (p <0.01).

To determine whether activation of JAK/STAT6 signal pathway is responsible for IL-13-induced PDGF production, primary cultured airway fibroblasts were pretreated with JAK inhibitor A77 1726 (50 μM) for 1 h before stimulation of cells with 100 ng/mL IL-13 for 24 h. Figure 3C shows that inhibition of JAK dramatically reduced IL-13-induced PDGF-AA production (p<0.01), suggesting that JAK/STAT6 signal pathway particularly mediated IL-13-induced PDGF expression.

3.4 *PDGF and resultant ERK1/2 MAPK activation mediates IL-13-induced collagen I production in airway fibroblasts*

To determine whether IL-13-induced PDGF plays a role in collagen I production in airway fibroblasts, primary cultured airway fibroblasts were prior treated with PDGF receptor blocker trapidil (1 mM) for 1 h before stimulation of cells



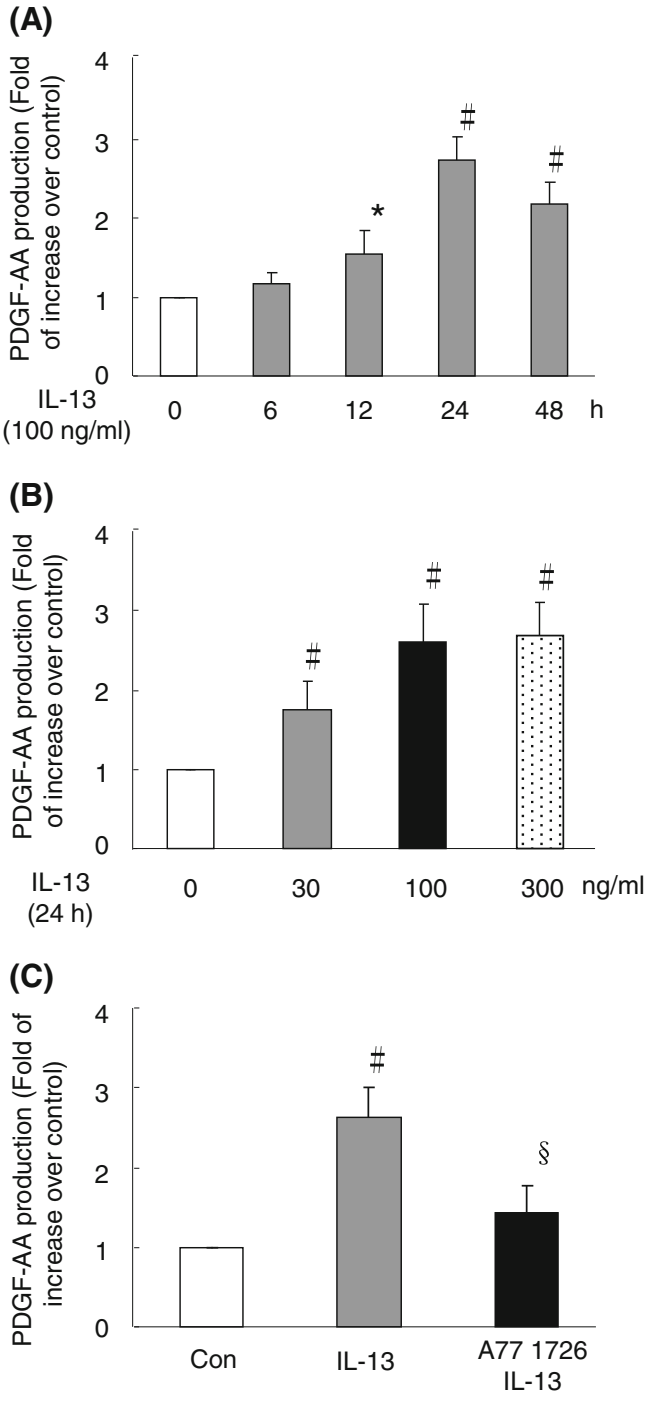
◀ **Figure 2.** JAK/STAT6 signalling mediates the effect of IL-13 on collagen I production in primary cultured airway fibroblasts. (**A**) Airway fibroblasts were stimulated with 100 ng/ml IL-13 for different time. Phosphorylation of STAT6 was determined in cell lysates using immunoblotting. Representative Western blot and quantification of bands are shown (n=4 each group). (**B**) Cells were treated with different concentrations of IL-13 for 15 min, and STAT6 phosphorylation was examined in cell lysates using Western blotting (n=4 each group). (**C**) Cells were prior treated with JAK inhibitor A77 1726 (50 μM) for 1 h before stimulation of cells with 100 ng/mL IL-13 for 48 h. Conditioned medium was collected to determine the level of collagen I using ELISA (n=4 each group). *p<0.05, #p<0.01 versus control cells (Con); §p<0.01 versus IL-13-stimulated cells (IL-13).

with 100 ng/mL IL-13 for 48 h; the level of collagen I in conditioned medium was measured using ELISA. Figure 4 indicates that blocking PDGF receptor partially suppressed IL-13-induced collagen I production (p <0.05 versus IL-13-stimulated cells alone).

To clarify the signalling mechanisms responsible for induction of PDGF causing collagen I production, airway fibroblasts were stimulated with IL-13 (100 ng/mL) for different times and the level of ERK1/2 phsophorylation was determined. As shown in figure 5A, 100 ng/mL IL-13 time-dependently induced ERK1/2 phosphorylation; the peak time for IL-13 induction of ERK1/2 phsophorylation was 24 h, suggesting that the activation of ERK1/2 might be mediated by another mediator induced by IL-13.

To further examine whether JAK/STAT6 signalling cascade and PDGF were involved in ERK1/2 phosphorylation induced by IL-13, airway fibroblasts were prior treated with JAK inhibitor A77 1726 (50 μM) or PDGF receptor blocker trapidil (1 mM) for 1 h and followed by the IL-13 (100 ng/mL) stimulation for 24 h. Figure 5B indicates that IL-13 induced a significant ERK1/2 phosphorylation, and this effect was suppressed by either JAK inhibitor or PDGF receptor blocker (p<0.01 versus IL-13-stimulated cells), suggesting that activation of JAK/STAT6 and resultant PDGF induction by IL-13 was implicated in ERK1/2 phosphorylation.

To clarify whether JAK/STAT6, PDGF and ERK1/2 MAPK were sequentially involved in collagen I generation caused by IL-13, airway fibroblasts were prior incubated with JAK inhibitor A77 1726 (50 μM), PDGF receptor blocker trapidil (1 mM) or MEK (up-stream activator of ERK1/2) inhibitor PD98 059 (50 μM) for 1 h, followed by treatment of cells with IL-13 (100 ng/mL) for 48 h, and the level of collagen I in conditioned medium was measured. As shown in figure 5C, pre-treatment of cells with JAK inhibitor, PDGF receptor blocker or MEK inhibitor partially suppressed IL-13-induced collagen I production, which declined from 2.44-fold increase over control in IL-13 stimulated cells to 1.63- (p<0.01), 1.99- (p<0.05) and 2.01-fold



◀**Figure 3.** IL-13 stimulates PDGF production by activation of JAK/STAT6 cascades in primary cultured mouse airway fibroblasts. (**A**) Time course of PDGF-AA production stimulated by IL-13 (100 ng/mL). PDGF-AA in conditioned medium was determined using ELISA (n=4 each group). (**B**) Dose responsive study of PDGF-AA in response to IL-13 at 24 h (n=4 each group). (**C**) Cells were pretreated with JAK inhibitor A77 1726 (50 μM) for 1 h before stimulation of cells with 100 ng/ml IL-13 for 24 h, level of PDGF-AA was measured in conditioned medium (n=4 each group). *p<0.05, #p<0.01 versus control cells (Con); §p<0.01 versus IL-13-stimulated cells (IL-13).

(p<0.05) increase over control, respectively, indicating that all above signal mechanisms coordinate and cause collagen I production in IL-13-stimulated airway fibroblasts.

4. Discussion

Elevation of IL-13 has been reported in a variety of asthma models and patients with asthma (Kim *et al.* 2010; Corren *et al.* 2011; Elias and Lee 2011; Jing *et al.* 2012). The pathogenesis of IL-13 in development of asthma includes: (a) evoking airway inflammation and causing airway hyperresponsiveness, and (b) inducing airway remodelling by stimulating proliferation of airway smooth muscle cells and fibroblasts and excessive deposition of ECM, particularly collagen (Elias and Lee 2011). Inhibition of IL-13 by blocking peptide has been shown to suppress OVA-induced airway fibrosis by reducing collagen production (Yang *et al.* 2004; Ma *et al.* 2013). Further study indicates that IL-13 stimulates collagen I production in airway fibroblasts derived from patients of asthma (Firszt *et al.* 2014). Yet, the molecular mechanisms underlying this effect are still largely unclear. The present study found that activation of JAK/STAT6 signalling pathway specifically mediated IL-13-induced collagen I production in primary cultured mouse airway fibroblasts, since this effect was significantly blocked by prior treatment of cells with JAK inhibitor A77 1726 (figure 6).

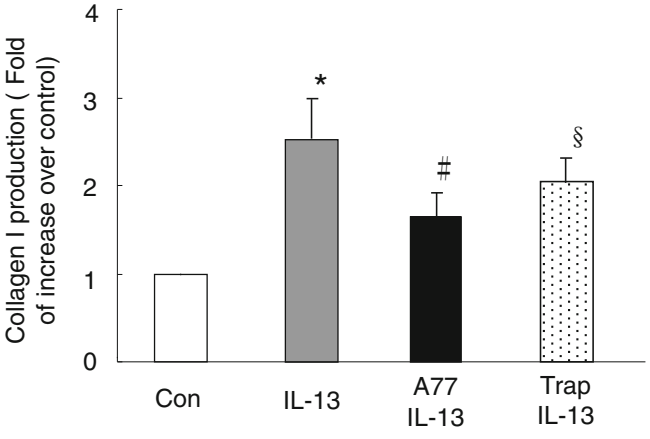
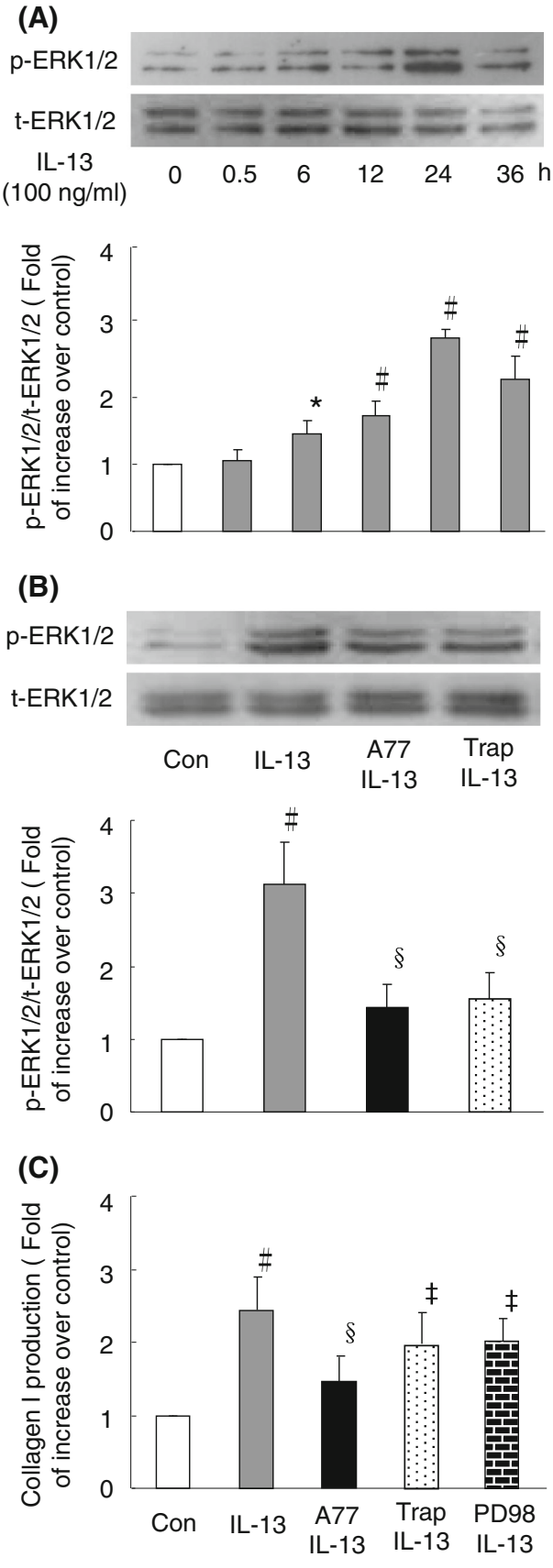


Figure 4. Induction of PDGF mediates IL-13-triggered collagen I production in airway fibroblasts. Cells were pre-exposured to JAK inhibitor A77 1726 (50 μM), or PDGF receptor blocker trapidil (1 mM) for 1 h before stimulation of cells with 100 ng/ml IL-13 for 48 h; conditioned medium was used for collagen I assay (n=4 each group). *p<0.01 versus control cells (Con); #p<0.01, §p<0.05 versus IL-13-stimulated cells (IL-13).



◀ **Figure 5.** PDGF-stimulated ERK1/2 activation mediates IL-13-induced collagen I production in primary cultured airway fibroblasts. (**A**) Time course of ERK1/2 phosphorylation stimulated by IL-13 (100 ng/mL). Phosphorylation of ERK1/2 was determined in cell lysates using immunoblotting (n=4 each group). (**B**) Cells were pre-incubated with JAK inhibitor A77 1726 (50 μM), or PDGF receptor blocker trapidil (1 mM) for 1 h before stimulation of cells with 100 ng/mL IL-13 for 24 h. ERK1/2 phosphorylation was determined using immunoblotting (n=4 each group). (**C**) Cells were prior treated with JAK inhibitor A77 1726 (50 μM), PDGF receptor blocker trapidil (1 mM) or MEK inhibitor PD98 059 (50 μM) for 1 h and followed by simulation of cells with 100 ng/mL IL-13 for 48 h; conditioned medium was used for collagen I assay (n=4 each group). *$p<0.05$, #$p<0.01$ versus control cells (Con); §$p<0.01$, ‡$p<0.05$ versus IL-13-stimulated cells (IL-13).

Phosphorylation of STAT6 results in dimerization and translocation of STAT6 into nucleus, where it activates transcription of particular genes containing specific interferon-gamma-activated site (GAS)-like sequences (Chen *et al.* 2011b). Several studies have shown that PDGF is an important target gene of STAT6, and induction of PDGF plays a critical role in wound healing, cell malignancy and fibrosis diseases by stimulating cell proliferation, migration and production of ECM (Ostendorf *et al.* 2012; Chen *et al.* 2011a). A recent study by Ingram has shown that IL-13 stimulates PDGF production in mouse pulmonary fibroblasts by activation of JAK/STAT6 signal pathway (Ingram *et al.* 2006). However, it is unknown whether up-regulation of PDGF by JAK/STAT6 cascade stimulates collagen I production in airway fibroblasts to contribute to airway remodelling of asthma. The present study indicated that the level of PDGF and collagen I in conditioned medium of primary

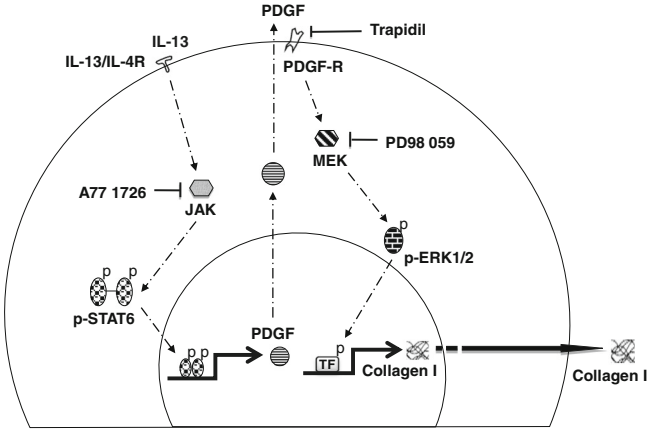


Figure 6. Proposed mechanism of IL-13-triggered collagen I production in primary cultured airway fibroblasts. Activation of STAT6 mediates IL-13 induction of PDGF. Elevation of PDGF further stimulates ERK1/2 MAPK-dependent production of collagen I. TF: transcriptional factor.

cultured airway fibroblasts was dramatically increased in presence of IL-13, and the elevation of PDGF and collagen I was substantially blocked by the JAK inhibitor, suggesting that JAK/STAT6 signalling cascade mediated IL-13-induced PDGF and collagen I production.

PDGF has multiple functions and is associated with the development of a variety of diseases in mammals (Hao *et al.* 2012; Ostendorf *et al.* 2012). It has also been shown that PDGF induces cardiac fibroblasts proliferation and collagen production by activating the ERK1/2 signal pathway (Zhang *et al.* 2011). In the present study, we used PDGF receptor blocker trapidil to examine whether overproduction of PDGF was involved in IL-13-induced collagen generation. Our results indicated that the presence of trapidil partially suppressed IL-13 stimulated collagen I production in airway fibroblasts, and we also found that trapidil inhibited IL-13 stimulated ERK1/2 phosphorylation. More importantly, the presence of MEK inhibitor PD98 059 also partially suppressed IL-13-caused collagen I production. Our study suggests that except IL-13-induced PDGF production and ERK1/2 MAPK activation, other mechanisms might also participate in IL-13-stimulated collagen I generation.

In this study, we demonstrated that IL-13 stimulated collagen I production in primary cultured mouse airway fibroblasts by activating JAK/STAT6 signal pathway to generate PDGF and the resultant activation of ERK1/2 MAPK signalling. Our study provided novel molecular mechanisms by which IL-13 stimulated airway remodelling – targeting these signal pathways might have potential value in ameliorating airway remodelling and benefits asthma.

Acknowledgements

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