Platelet-derived growth factors (PDGFs) mediate tissue repair and wound healing. PDGFs are synthesized and secreted by most inflammatory cell types present within the milieu of the asthmatic airway. We have previously reported that airway fibroblasts from severe asthmatics produce more type I procollagen in response to PDGF stimulation as compared to patients with mild asthma and normal control subjects; therefore, we hypothesized that the enhanced responsiveness to PDGFs in patients with severe asthma is linked to an increased expression of PDGF receptors. In an ongoing study, 5 subjects with severe asthma, 10 subjects with mild-to-moderate asthma, and 6 normal control subjects underwent bronchoscopy with endobronchial biopsy. Biopsies were placed in Dulbecco’s modified Eagle’s serum supplemented with fetal bovine serum (10%), streptomycin (100 µg/mL), penicillin (10,000 U/mL), and gentamicin (100 µg/mL), and cultured until fibroblast growth was established at ≥50% confluency (approximately 8 to 20 days). Immunostaining with vimentin (Dako; Carpinteria, CA) and α-smooth muscle actin (Dako) confirmed fibroblast identity. To determine baseline fibroblast expression of PDGF receptors (PDGFRs) [PDGFR-α and PDGFR-β], we developed a sandwich enzyme-linked immunosorbent assay for these receptors that quantifies receptor protein levels in fibroblast cell lysates. Receptor protein levels were expressed in nanograms per 100 µg of total cell protein. There were no significant differences in baseline expression of PDGFR-α between the groups (severe, 7.6 ng/100 µg protein; mild to moderate, 12.50 ng/100 µg protein; normal control, 11.33 ng/100 µg protein; p = 0.35). However, there was a significantly greater baseline expression of PDGFR-β in the severe asthmatic group, as compared to both the mild/moderate asthmatic and normal control groups (severe, 15.20 ng/100 µg protein; mild to moderate, 13.30 ng/100 µg protein; normal control, 3.67 ng/100 µg protein; p = 0.0024). Our data suggests that airway fibroblasts from severe asthmatics may be of a synthetic phenotype, with altered capabilities in collagen production, as compared to those from patients with mild-to-moderate asthma and normal control subjects, and this may be driven by an increased expression of PDGFR-β.

Modulation of Fibroblast Growth Factor Expression and Signal Transduction in Type II Cells*

Cheng-Ming Li, MD, PhD; Donna Newman, PhD; Mark Cesta, DVM; Leslie Tompkins, BS; Jody Khosla, MS; and Philip L. Sannes, PhD

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Abbreviations: ECM = extracellular matrix; FGF = fibroblast growth factor

Fibroblast growth factors (FGFs) influence lung epithelial cells in processes relating to maintenance and repair following injury. Their role in chronic conditions such as asthma is largely unknown, but likely involves fundamental relationships between epithelium and the underlying extracellular matrix (ECM) and fibroblasts. FGFs utilize complex interactions between ECMs (e.g., heparan sulfate proteoglycans), soluble cell factors (FGF-binding proteins), and relevant sequential signaling cascades. This relationship affords a crucial role for heparan sulfate proteoglycans, whose sulfated character are differentially expressed in ECMs where they are known to be potent biological modifiers. The goal of this study was to determine whether specific signaling pathways relating to FGF-1 and FGF-2 and expression of selected genes were altered by the model ECM heparin. Phosphorylation (p) of extracellular signal-regulated kinase-1/extracellular signal-regulated-2 was found to be reduced by 500 µg/mL of heparin in type II cells stimulated with 50 to 100 ng/mL of FGF-1 or FGF-2 at 15 min. p-RAF was elevated by low concentrations of heparin with FGF-1 but reduced by heparin with FGF-2. p-e-Myc was reduced by high heparin but elevated by low heparin with FGF-1; 500 µg/mL of heparin down-regulated gene expression of FGF-1, FGF-2, and FGF-7, FGF receptor-2, and FGF binding protein, but not FGF-1, in type II cells with and without treatment with FGF-1 or FGF-2. Culture of type II cells with fibroblasts resulted in reduced expression in the former of FGF-1 and FGF-2, and FGF receptor-2(IIIb), but not FGF-1 or FGF-2, and elevation of FGF binding protein. These results demonstrate important regulatory links between FGFs and sulfated ECMs and implicate key interactions between type II cells and fibroblasts in the modulation of airway/alveolar diseases in the lung.

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Correspondence to: Monica Kraft, MD, FCCP, National Jewish Medical and Research Center, 1400 Jackson St, B-120, Denver, CO 80206; e-mail: kraftm@ujc.org

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Correspondence to: Philip L. Sannes, PhD, Veterinary Medicine, NCSU, 4700 Hillsborough St, Raleigh, NC 27606; e-mail: philip_sannes@ncsu.edu