American Journal of Pathology, Vol. 149, No. 2, August 1996

Platelet-Derived Growth Factor Causes Pulmonary Cell Proliferation and Collagen Deposition *in Vivo*

Eunhee S. Yi, Hyesun Lee, Songmei Yin,[†] Pierre Piguet,[†] Ildiko Sarosi,[†] Steve Kaufmann,[†] John Tarpley,[†] Nai-San Wang,[‡] and Thomas R. Ulich[*†]

From the Department of Pathology,[*] University of California at San Diego, School of Medicine, San Diego, California; Amgen, Inc.,[†] Thousand Oaks, California; and the Department of Pathology,[‡] University of California at Irvine, School of Medicine, Irvine, California

Platelet-derived growth factor (PDGF) is postulated to play a role in the pathophysiology of pulmonary fibrosis. Recombinant human PDGF-BB administered as a single intratracheal injection in rats causes an increase in peribronchial and perivascular stromal cells on days 2 and 3 after injection as evaluated by hematoxylin and eosin histology and 5-bromodeoxyuridine incorporation. Proliferation of bronchial epithelial cells and arterial smooth muscle cells, although not evident by routine histological examination alone, is detected on days 2 and 3 by increased 5-bromodeoxyuridine incorporation. A mild increase in 5-bromodeoxyuridine labeling is observed in peripheral alveolar parenchyma after injection of PDGF. The proliferative peribronchial and perivascular mesenchymal cells appear by light microscopic and ultrastructural criteria to be fibroblasts that are immunoreactive for vimentin but negative for α-smooth muscle actin and desmin. Daily intratracheal injection of PDGF-BB for 3 days causes a slightly more pronounced peribronchial and perivascular spindle cell proliferation accompanied by collagen deposition as evaluated by Masson's trichrome stain. PDGF-induced increases in cellularity and collagen resolve within 5 days after the last PDGF injection. In conclusion, intratracheal injection of PDGF-BB causes transient proliferation of pulmonary mesenchymal and epithelial cells accompanied by collagen deposition. (Am J Pathol 1996, 149:539–548)

Platelet-derived growth factor (PDGF) is a potent mitogen and chemoattractant for mesenchymal cells and induces gene expression of cell matrix-related molecules such as fibronectin, collagen, and glycosaminoglycans.[1] Structurally, PDGF forms a dimeric molecule consisting of A and B chains that are approximately 60% homologous at the amino acid level.[2] PDGF-AB heterodimer predominates in human platelets whereas PDGF-BB homodimer prevails in serum and platelets of most nonhuman species.[1]

PDGF induces diverse functions by binding to specific high-affinity cell surface receptors.[3] The PDGF receptors belong to a family of tyrosine kinases that consist of α- and β-subunits in three possible combinations: αα, αβ, and ββ.[4] The α-receptor subunit can bind to either the A or B chain of PDGF, whereas the β-subunit is capable of binding only to the PDGF-B chain.[4] Thus, the PDGF-BB used in the present study should be able to act upon target cells bearing any type of PDGF receptor. PDGF receptors have been found on most mesenchymal cells including fibroblasts, osteoblasts, chondroblasts, smooth muscle cells, glial cells, and capillary endothelial cells.[5] Although epithelial cells have been generally considered to be unresponsive to PDGF, there have been recent studies reporting PDGF receptor expression in human lung carcinoma cell lines,[6,7] skin epithelial cells,[8] mouse mammary epithelial cell lines,[9] and fetal rat lung epithelial cells.[5]

Abnormal expression of PDGF has been postulated to play an important role in idiopathic or secondary fibrotic lung diseases. PDGF has also been suggested to contribute to tumor growth and to the stromal reaction surrounding lung carcinomas.[10–14] In this study, exogenous PDGF is demonstrated to exert a trophic effect upon pulmonary epithelial and mesenchymal cells *in vivo*.

Accepted for publication March 29, 1996.

Address reprint requests to Dr. Thomas R. Ulich, Amgen, Inc., 1840 DeHavilland Drive, MS 15-2-250, Thousand Oaks, CA 91320.

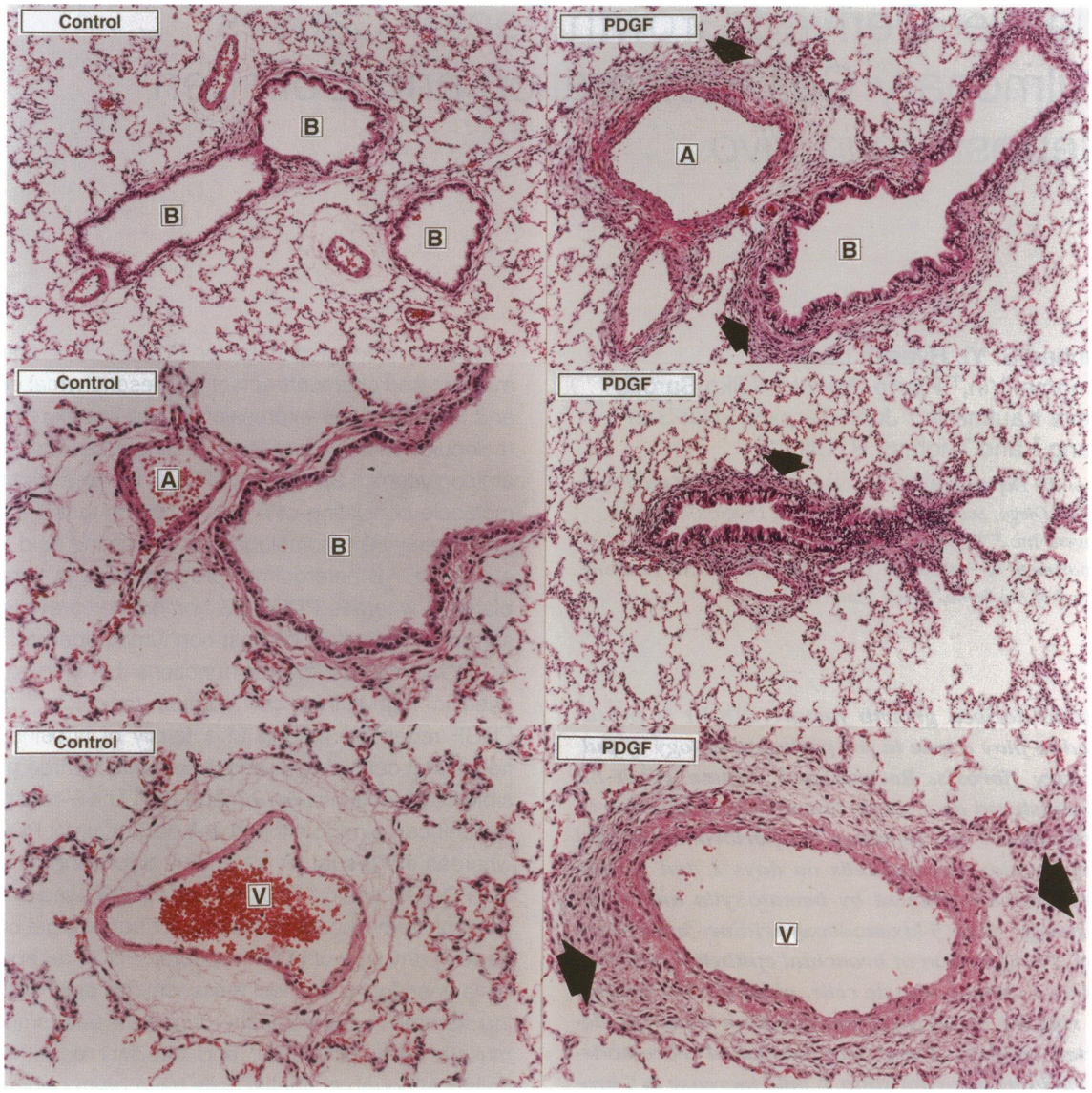

Figure 1. *Peribronchial and perivascular stromal cell hyperplasia* (**arrows**) *is evident 3 days after a single i.t. injection of PDGF* (**right column**). *The paucity of cells in normal perivascular or peribronchial spaces in saline-injected control rats is illustrated in the* **left column**. *PDGF-induced bronchial epithelial cell hyperplasia is suggested by a nuclear crowding in bronchial mucosal cells of PDGF-treated rats as compared with controls. Bronchial, arterial, and venous lumens are labeled as B, A, and V, respectively. H&E stain.*

Materials and Methods

Injection of Rats with Intratracheal and Intravenous PDGF

Pathogen-free male Lewis rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing approximately 225 g were injected intratracheally (i.t.) with recombinant human PDGF-BB at a dose of 0.6 mg/rat in 0.5 ml of phosphate-buffered saline (PBS). The recombinant PDGF-BB (Amgen, Thousand Oaks, CA) contained less than 2.5 EU/ml. Control rats received an i.t. injection of the same volume of PBS or bovine serum albumin diluted in PBS. After a single i.t. instillation (n = 19 rats receiving PDGF; n = 14 controls) or three consecutive daily i.t. instillations (n = 15 rats receiving PDGF; n = 14 controls), the rats were sacrificed at various time points ranging from 1 to 5 days. 5-Bromodeoxyuridine (BrdU) at a dose of 12.5 mg/rat was injected in selected rats (PDGF or control (n = 3 each)) at days 1, 2, and 3 (total n = 18) at 24 hours before sacrifice, and BrdU incorporation was detected immunohistochemically with anti-BrdU antibody (Amersham, Arlington Heights, IL) as an indication of *in vivo* DNA synthesis. Intravenous PDGF-BB was injected at doses of 0.5 (n = 10) and 1 (n = 10) mg/rat either once or three times a week for 10 weeks. Control rats (n = 10) received intravenous saline three times a week for 10 weeks.

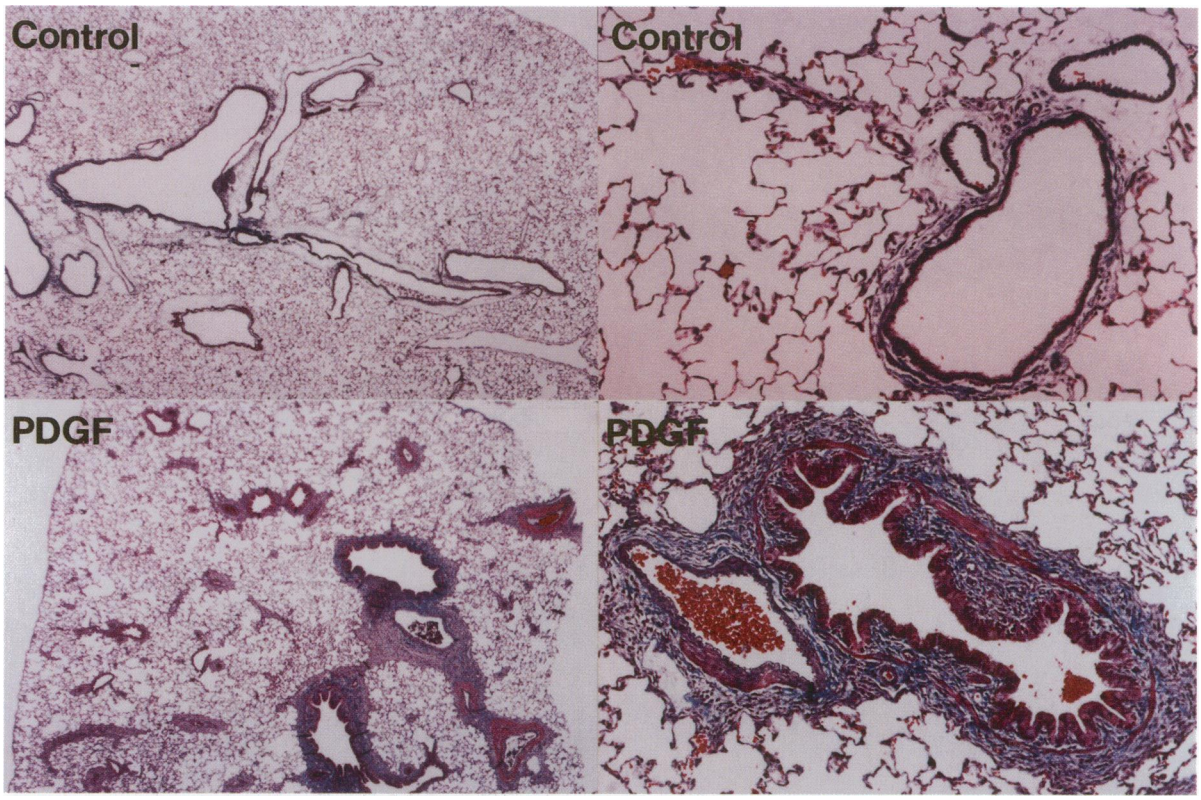

Figure 2. *The lungs of PDGF-treated rats show an increased deposition of peribronchial and perivascular collagen (blue staining in* **lower two panels**) *as compared with control lungs* (**upper panels**). *Masson's trichrome stain.*

Histology, Immunohistochemistry, and Ultrastructural Study

The lungs were removed *in toto* at the time of sacrifice and fixed overnight after infusion of 15 ml of 10% neutral buffered formalin via the trachea to inflate alveoli. Lung sections for histological examination and BrdU counting were taken at the midsaggital plane of the right and left lungs encompassing the largest surface area. Formalin-fixed, paraffin-embedded lung sections were examined with hematoxylin and eosin (H&E) and Masson's trichrome stains. Immunohistochemical staining was performed on selected paraffin-embedded tissues using primary antibodies against α-smooth muscle actin (Dako, Carpinteria, CA), desmin (Dako), and vimentin (BioTek Solutions, Santa Barbara, CA) followed by biotinylated secondary antibody and 3,3′-diaminobenzidine tetrachloride (Sigma Chemical Co., St. Louis, MO) as a chromogen with the standard avidin-biotin complex method as previously described.[15] An alkaline phosphatase detection system was used for anti-BrdU antibody. A transmission electron microscopic study was performed on selected lung tissues after the examination of plastic-embedded 1-μm-thick toluidine-blue-stained sections.

Quantitation of BrdU Incorporation

BrdU labeling index was quantitated separately in bronchial epithelial cells, peribronchial and perivenular mesenchymal cells, and pulmonary arterial smooth muscle cells by light microscopic examination. The number of BrdU-stained nuclei in the 10 most prominently labeled bronchi, peribronchial, and perivenular spaces and pulmonary arteries were counted using the 20× objective lens. The average numbers out of BrdU-labeled cells in 10 structures (BrdU counts/anatomical structure) are presented separately for each compartment. The average BrdU counts in peripheral alveolar parenchyma were obtained by counting BrdU-stained nuclei in 10 random noncontiguous high power fields (40× objective lens) and presented as BrdU counts/field. BrdU-positive cells were counted in the 10 most prominently labeled bronchovascular structures in each section of lung for the following two reasons: 1) not every labeled cell in each anatomic structure in each bronchovascular structure in each midsaggital section could be counted because of the laborious nature of the task, and 2) the mean labeling of cells in all bronchovascular structures would have been a misleading number as some structures did not contain any labeled cells. The absence of proliferation in these

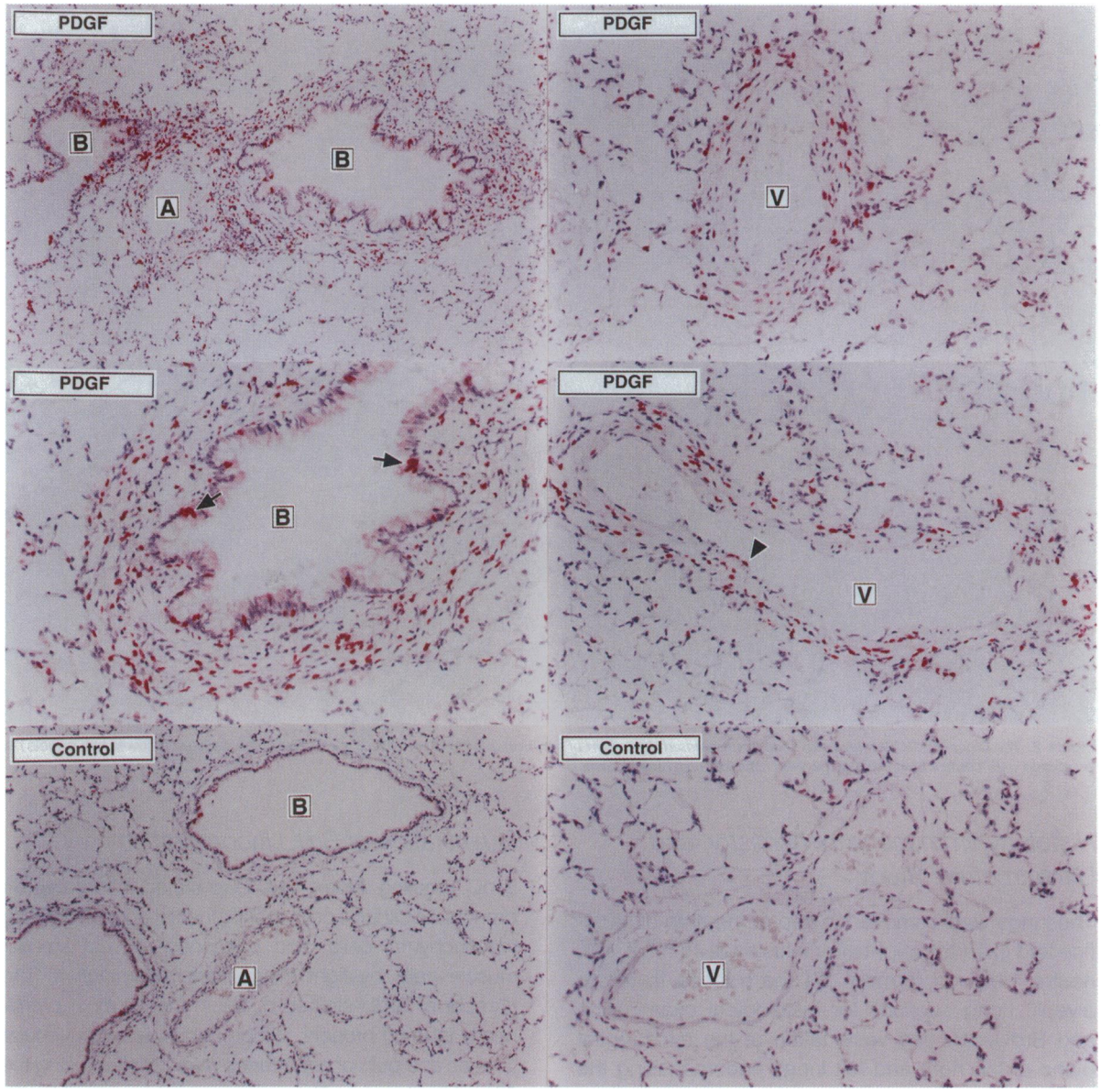

Figure 3. *PDGF-induced BrdU incorporation is mainly localized in bronchial epithelial cells* (**arrows**) *and stromal cells surrounding bronchi* (*B*), *arteries* (*A*), *and veins* (*V*). *Some arterial smooth muscle cells and a few venous endothelial cells* (**arrowhead**) *also show positive BrdU staining. Saline-injected control rats* (**bottom panels**) *show little or no BrdU labeling. Anti-BrdU stain.*

unlabeled structures, however, in our opinion represents the liklihood that i.t. instillation does not provide a completely uniform distribution of administered protein throughout the lung and therefore PDGF never reached these structures. The data are presented as the mean ± 1 SD of the mean. The probability value was determined by the two-tailed *t*-test (Systat, Evanston, IL).

Results

The most striking histological feature after i.t. instillation of PDGF was an increase in peribronchial and perivascular mesenchymal cells (Figure 1). Mitoses were occasionally seen in the peribronchial and perivascular mesenchymal cells of PDGF-treated rats. Cellular proliferation in peripheral alveolar parenchyma was not remarkable by H&E histology. Daily injection of PDGF for 3 consecutive days also caused a similar or slightly more pronounced degree of histological changes as for a single injection. Peribronchial and perivascular collagen deposition was demonstrated by Masson's trichrome stain (Figure 2). The histological changes induced by either single or daily PDGF injections were no longer evident 5 days after the last PDGF injection.

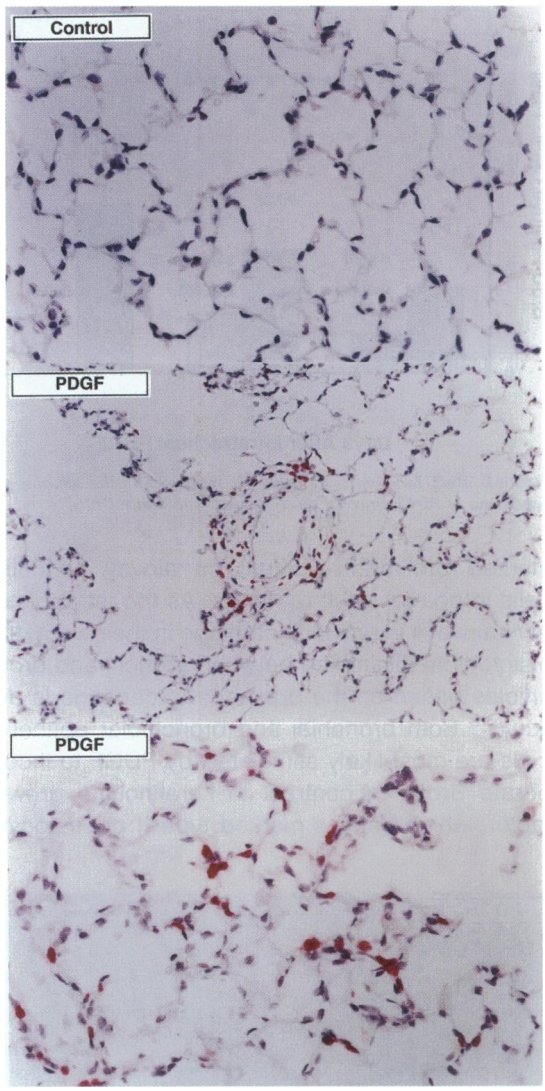

Figure 4. *Saline-injected control rats* (top panel) *show little or no BrdU incorporation in the alveolar parenchyma. In contrast, PDGF-injected lungs show frequent BrdU-positive cells in the alveoli as well as in the adventitia of small venules* (middle panel). *Anti-BrdU stain.*

A single i.t. injection of PDGF-BB into rats caused marked increases in BrdU incorporation in bronchial epithelial cells, peribronchial and perivenular mesenchymal cells, and pulmonary arterial smooth muscle cells at days 2 and 3 as compared with control rats (Figures 3 to 5). PDGF-injected lungs at 2 days contained greater than 10 BrdU-positive bronchial epithelial cells in 77.6 ± 6.6% of bronchi/lung section as compared with 7.3 ± 5.3% in control lungs ($P < 0.0001$). Thus, PDGF-induced BrdU incorporation was noted in approximately 70% of bronchovascular structures in any given midsaggital section. Arterial endothelial cells generally did not show BrdU uptake, whereas venular endothelial cells occasionally showed BrdU incorporation (Figure 3). BrdU labeling in bronchial epithelial cells appeared to peak at day 2, whereas BrdU labeling of mesenchymal and smooth muscle cells peaked at days 2 to 3 (Figure 5). At days 1 to 3, peripheral alveolar parenchyma of PDGF-injected rats also showed an increase in BrdU-labeled cells (Figures 4 and 6) that are composed of spindle-shaped interstitial cells and occasional alveolar epithelial cells. Peribronchial lymphoid tissue in PDGF-injected and control rats showed no significant differences in BrdU incorporation at any time points (data not shown).

The proliferating mesenchymal cells around bronchi and vessels were composed of fibrocytic cells that are diffusely positive for vimentin but negative for α-smooth muscle actin and desmin on immunohistochemical staining (Figures 7 and 8). On electron microscopic examination, the new stromal cells showed features of fibroblasts characterized by spindle-shaped cells with abundant branching rough endoplasmic reticulum (Figure 9). Occasional neutrophils, lymphocytes, eosinophils, and mast cells were also present. Scattered collagen fibers were noted in intercellular spaces (Figure 9).

The potential effect of systemic PDGF on the lung was tested by intravenous administration of PDGF at doses of 0.5 and 1 mg/rat either once or three times a week for 10 weeks. PDGF given systemically in this fashion did not cause any mesenchymal or epithelial cell proliferation in the lung as judged histologically either by H&E-stained sections or by BrdU incorporation.

Discussion

Recombinant human PDGF-BB administered as a single i.t. injection in rats caused an increase in peribronchial and perivascular stromal cells on days 2 and 3 after injection as evaluated by H&E histology. BrdU incorporation into bronchial epithelial cells, peribronchovascular mesenchymal cells, and vascular smooth muscle cells was remarkably increased in PDGF-injected rats as compared with control rats that show little or no BrdU labeling in the lung. The PDGF-induced increase of BrdU labeling in the peripheral alveolar parenchyma is significant but is not as obvious as in the bronchial or vascular compartments. Intravenous administration of PDGF caused neither histologically discernible pulmonary cell proliferation nor increased BrdU incorporation in the lung.

PDGF is well recognized as a potent mitogen for cells of mesenchymal origin, but recent findings

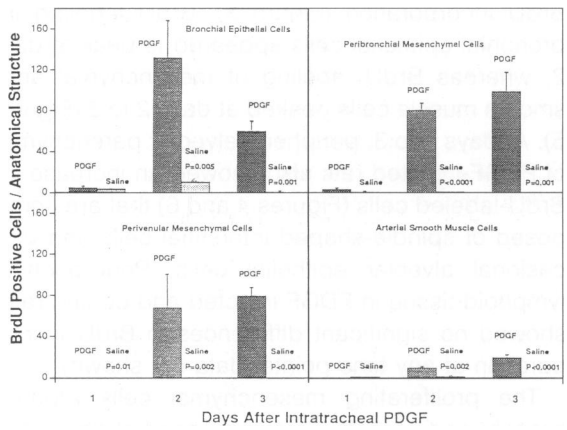

Figure 5. *BrdU labeling peaks at day 2 in bronchial epithelial cells and at days 2 to 3 in peribronchovascular stromal cells and vascular smooth muscle cells.*

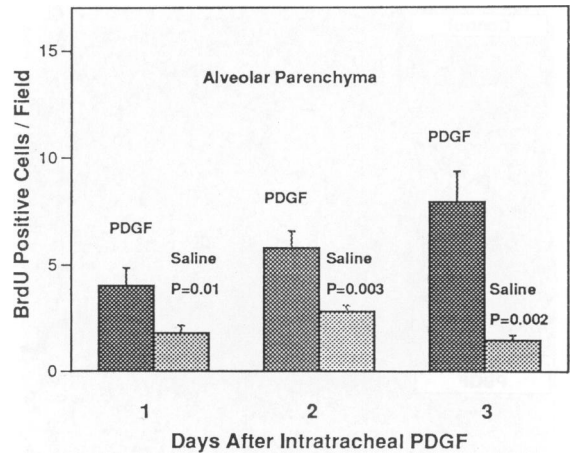

Figure 6. *BrdU labeling is significantly increased in the alveolar parenchyma of PDGF-injected as compared with control rats.*

indicate that it may also induce the growth of some epithelial cells.[5–8] A previous study reported that exogenous PDGF is a direct mitogen for fetal lung epithelial cells by demonstrating a dose- and time-dependent stimulatory effect of PDGF-AA and -BB on epithelial cell [^{3}H]thymidine incorporation that was abrogated by preincubation with an antibody against an extracellular domain of the rodent PDGF receptor.[5] Our study demonstrates a marked proliferative effect on airway epithelial cells in normal adult rat lungs. As the intrapulmonary airways in rats lack cartilage in their walls, the histological distinction between bronchi and bronchioles based on the presence of cartilage is difficult.[16] Both bronchial and bronchiolar epithelial cells are most likely stimulated by PDGF to incorporate BrdU. In contrast to keratinocyte growth factor, which causes marked type II pneumocyte

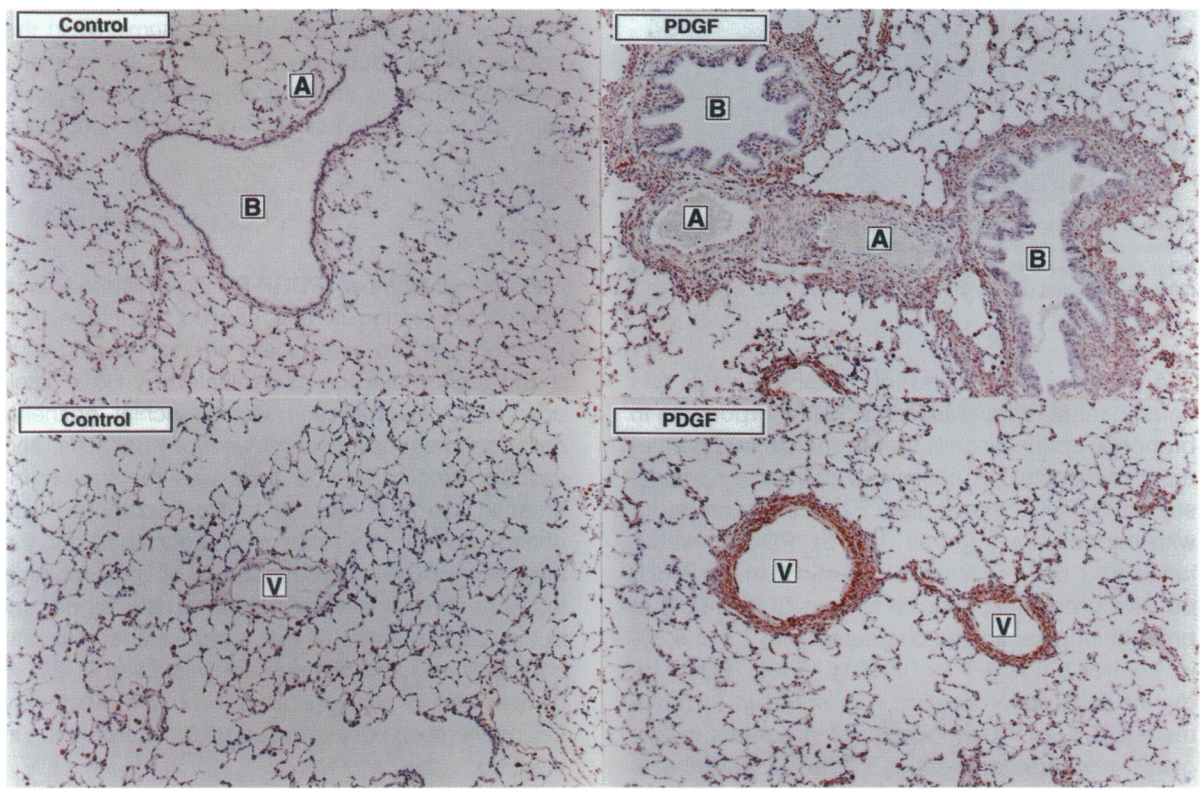

Figure 7. *The spindle cells in the peribronchial and perivascular spaces of PDGF-injected lungs are diffusely immunoreactive for vimentin, indicating a mesenchymal origin of these cells. B, bronchus; A, artery; V, vein. Anti-vimentin stain.*

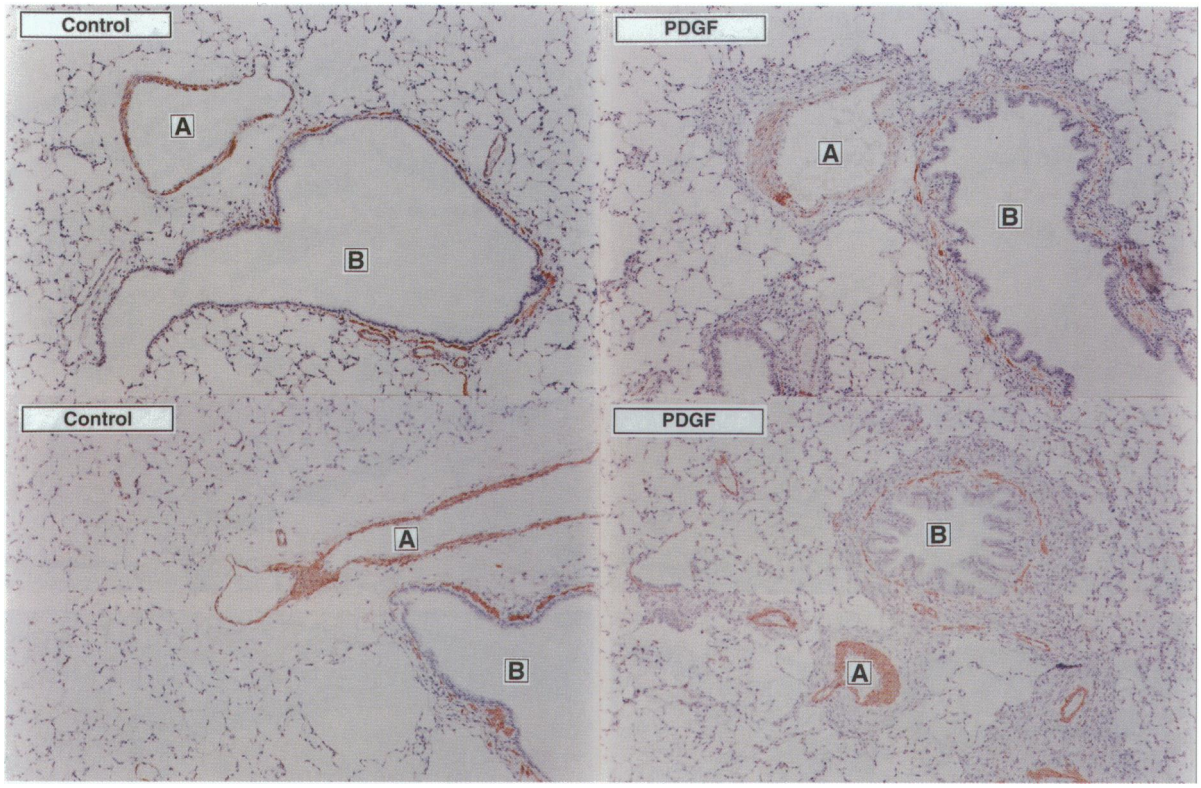

Figure 8. *The vimentin-positive stromal cells are negative for α-smooth muscle actin* (**top panel**) *and desmin* (**bottom panel**). *Bronchial and vascular smooth muscle cells serve as internal positive controls. B, bronchus; A, artery.*

hyperplasia as well as bronchial epithelial cell proliferation,[17] PDGF-BB does not cause striking type II pneumocyte hyperplasia.

PDGF-BB-induced fibroblastic proliferation and collagen fibrosis is mainly localized in the peribronchial and perivascular areas with relative sparing of alveolar septa. The accumulation of fibroblast-like cells in peribronchial and perivascular adventitia has been described as an early change in bleomycin-induced pulmonary fibrosis model.[18] A role for PDGF in the pathogenesis of idiopathic pulmonary fibrosis has been suggested by the up-regulation of PDGF gene expression and PDGF release in alveolar macrophages of patients.[19] Human PDGF-B overexpression in the lungs of Wistar rats after i.t. administration of an expression vector caused significant proliferation of fibroblasts and deposition of collagen in alveolar septa after 14 days.[20] In the same study, transforming growth factor-β was a more potent inducer of fibrosing alveolitis than PDGF, and transforming growth factor-β secondarily caused rat PDGF-B expression in the rat lung cells.[20]

Vimentin-positive, α-smooth-muscle-actin- and desmin-negative fibroblasts made up most of the peribronchial and perivascular proliferating mesenchymal cells after i.t. instillation of PDGF. Although the importance of myofibroblastic transformation during lung fibrosis has been reported by many investigators,[21–25] no significant myofibroblastic differentiation was observed in our material as judged by either immunohistochemistry or electron microscopy.

PDGF also caused BrdU incorporation in vascular smooth muscle cells. Less commonly, BrdU incorporation was noted in endothelial cells. PDGF receptors have been reported to be present in capillary endothelial cells.[26] Previous investigators such as Reidy et al and Libby et al have reported the expression of PDGF isotypes and their receptors in normal and injured vascular smooth muscle cells in balloon catheter injury and endothelial denudation models.[27–32] Antibody to PDGF has been reported to inhibit neointimal smooth muscle accumulation after angioplasty.[33] The nature of the PDGF-induced BrdU-positive cells in the peripheral alveolar parenchyma is not clear. As capillary endothelium and microvascular pericytes have been shown to express PDGF-β receptors,[34] these cells might participate in the response to PDGF. However, some cells appeared to be type II pneumocytes based on their cuboidal shape and typical location in the corners of alveoli.

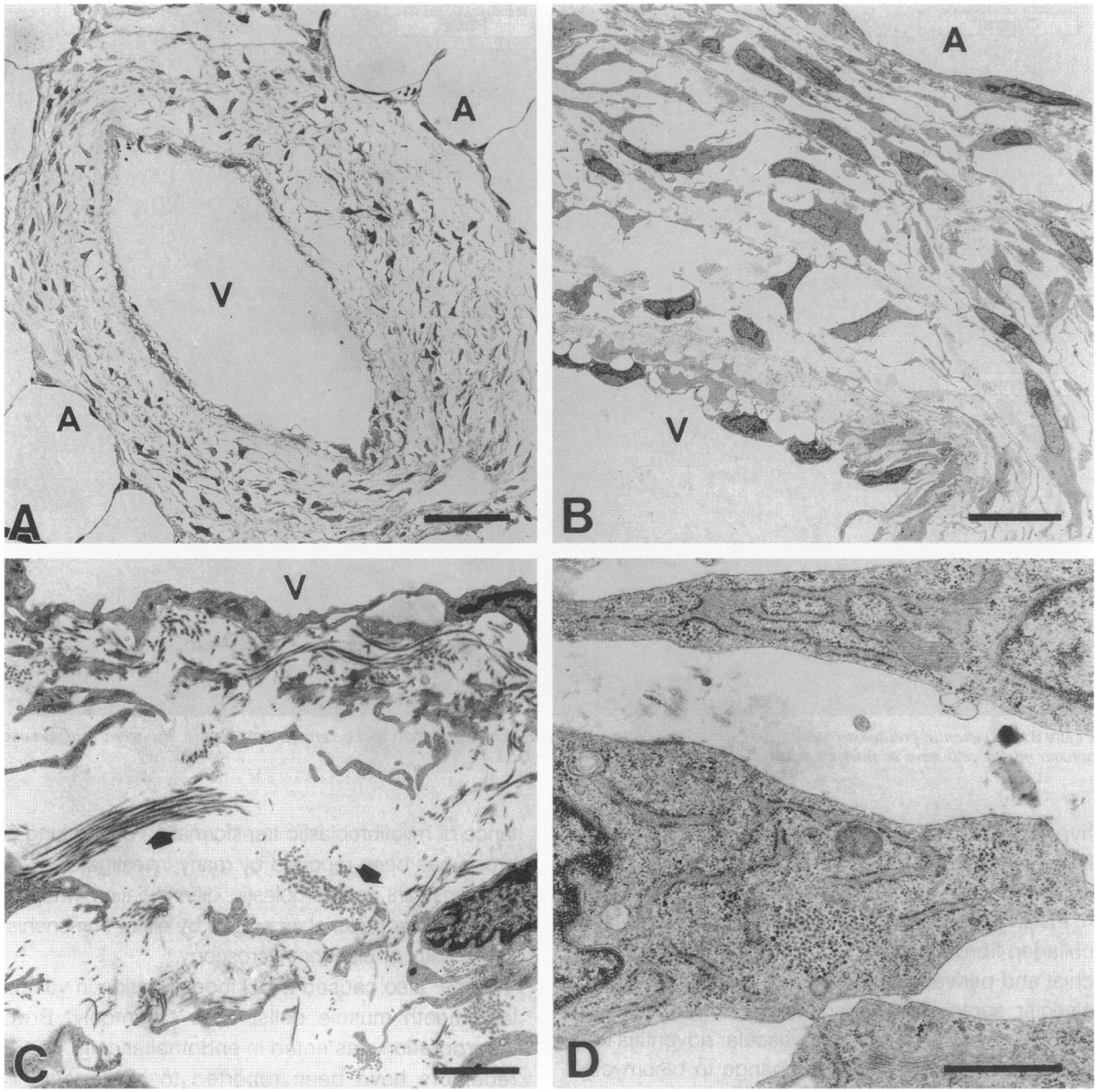

Figure 9. *PDGF-induced proliferation of mesenchymal spindle cells is illustrated in a perivenular space* (**A** *and* **B**). *A, alveoli; V, venular lumen. Occasional collagen fibers are present in the perivenular space* (**C**). *The PDGF-induced spindle cells appear to be fibroblasts with well developed rough endoplasmic reticulum* (**D**). *Peripheral actin microfilaments characteristic of myofibroblastic differentiation were not identified. Bars, 50 μm* (**A**), *10 μm* (**B**), *2 μm* (**C**), *and 1 μm* (**D**).

In summary, exogenous PDGF-BB administered i.t. into normal adult rats mainly causes proliferation of bronchial epithelial cells, peribronchial and perivascular mesenchymal cells, and vascular smooth muscle cells. Peribronchial and perivascular stromal cells reveal fibroblastic differentiation with intercellular collagen deposition. PDGF-induced fibroblastic proliferation and collagen fibrosis is reversible by 5 days after the cessation of PDGF stimulation. Repeated PDGF injections does not cause more than a slight increase in the degree of fibrosis as compared with a single PDGF injection. This might be partly due to the saturation of PDGF receptors in the target cells or to an unknown compensatory homeostatic mechanism. Conditions such as the intra-alveolar fibroblastic plugs in organizing pneumonia and the interstitial fibrosis in the organizing phase of diffuse alveolar damage are also reversible. The effects of exogenous PDGF on the lung *in vivo* support the hypothesis of previous authors that endogenous PDGF may play a role in the pathogenesis of pulmonary fibrosis. The observation that the proliferative effects of PDGF were seen after i.t. but not after

intravenous administration suggests that any effects of endogenous PDGF most likely would be mediated locally in a paracrine or autocrine fashion.

References

1. Fabisiak JP, Kelley J: Platelet-derived growth factor. Cytokines of the Lung. Edited by J Kelley. New York, Marcel Dekker, 1992, pp 3–39
2. Hart CE, Bailey M, Curtis DA, Osborn S, Raines E, Ross R, Forstrom JW: Purification of PDGF-AB and PDGF-BB from human platelet extracts and identification of all three PDGF dimers in human platelets. Biochemistry 1990, 29:166–172
3. Yarden Y, Escobedo JA, Kuang WJ, Yang-Feng TL, Daniel TO, Trembel PM, Chen EY, Ando ME, Harkins RN, Francke U, Fried VA, Ullrich A, Williams LT: Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors. Nature 1986, 323:226–232
4. Hart CE, Forstrom JW, Kelley JD, Seifert RA, Smith RA, Ross R, Murray MJ, Bowen-Pope DF: Two classes of PDGF receptor recognize different isoforms of PDGF. Science 1988, 240:1529–1531
5. Caniggia I, Liu J, Han R, Buch S, Funa K, Tanswell K, Post M: Fetal lung epithelial cells express receptors for platelet-derived growth factor. Am J Respir Cell Mol Biol 1993, 9:54–63
6. Forsberg K, Bergh J, Westermark B: Expression of functional PDGF β receptors in a human large cell lung carcinoma cell line. Int J Cancer 1993, 52:556–560
7. Antoniades HN, Galanopoulos T, Neville-Golden J, O'Hara CJ: Malignant epithelial cells in primary human lung carcinomas coexpress *in vivo* platelet-derived growth factor (PDGF) and PDGF receptor mRNAs and their protein products. Proc Natl Acad Sci USA 1992, 89:3942–3946
8. Antoniades HN, Galanopoulos T, Neville-Golden J, Kiritsy CP, Lynch SE: Injury induces *in vivo* expression of PDGF and PDGF receptor mRNAs in skin epithelial cells and PDGF mRNA in connective tissue fibroblasts. Proc Natl Acad Sci USA 1991, 88:565–569
9. Taverna D, Groner B, Hynes NE: Epidermal growth factor receptor, platelet-derived growth factor receptor, and c-*erb*B-3 receptor activation all promote growth but have distinctive effects upon mouse mammary epithelial cell differentiation. Cell Growth Differ 1991 2:145–154
10. Brandt-Rauf PW, Smith S, Hemminki K, Koskinen H, Vainio H, Niman H, Ford J: Serum oncoproteins and growth factors in asbestos and silicosis patients. Int J Cancer 1992, 50:881–885
11. Rom WN, Travis WD, Brody AR: Cellular and molecular basis of the asbestos-related diseases. Am Rev Respir Dis 1991, 143:408–422
12. Bravo M, Vasquez R, Rubio H, Salazar M, Pardo A, Selman M: Production of platelet-derived growth factor by human lung cancer. Respir Med 1991, 85:479–485
13. Vignaud JM, Marie B, Klein N, Plenat F, Pech M, Borrely J, Martinet N, Duprez A, Martinet Y: The role of platelet-derived growth factor production by tumor-associated macrophages in tumor stroma formation in lung cancer. Cancer Res 1994, 54:5455–5463
14. Bergh JCS: Gene amplification in human lung cancer: the *myc* family genes and other proto-oncogenes and growth factor genes. Am Rev Respir Dis 1990, 142: S20–S26
15. Pierce GF, Tarpley JE, Tseng J, Bready J, Chang D, Rudolph R, Robson M, Van de Berg J, Reed P, Kaufman S, Farrell K: Detection of platelet-derived growth factor (PDGF)-AA in actively healing human wounds treated with recombinant PDGF-BB and absence of PDGF in chronic nonhealing wounds. J Clin Invest 1995, 96:1336–1350
16. Sorokin SP: The respiratory system. Histology: Cell and Tissue Biology. Edited by L Weiss. New York, Elsevier Science Publishing, 1983, pp 814–817
17. Ulich TR, Yi ES, Longmuir K, Yin S, Blitz R, Morris CF, Housley R, Pierce GF: Keratinocyte growth factor is a growth factor for type II pneumocytes *in vivo*. J Clin Invest 1994, 93:1298–1306
18. Zhang K, Rekhter MD, Gordon D, Phan SH: Myofibroblasts and their role in lung collagen gene expression during pulmonary fibrosis: a combined immnunohistochemical and *in situ* hybridization study. Am J Pathol 1994, 145:114–125
19. Nagaoka I, Trapnell BC, Crystal RG: Upregulation of platelet-derived growth factor-A and -B gene expression in alveolar macrophages of individuals with idiopathic pulmonary fibrosis. J Clin Invest 1990, 85:2023–2027
20. Yoshida M, Sakuma J, Hayashi S, Abe K, Saito I, Harada S, Sakatani M, Yamamoto S, Matsumoto N, Kaneda Y, Kishimoto T: A histologically distinctive interstitial pneumonia induced by overexpression of the interleukin 6, transforming growth factor-β1, or platelet-derived growth factor B gene. Proc Natl Acad Sci USA 1995, 92:9570–9574
21. Leslie K, King TE, Low R: Smooth muscle actin is expressed by air space fibroblast-like cells in idiopathic pulmonary fibrosis and hypersensitivity pneumonitis. Chest 1991, 99:47S–48S
22. McDonald JA: Idiopathic pulmonary fibrosis: a paradigm for lung injury and repair. Chest 1991, 99:87S–93S
23. Fukuda Y, Ishizaki M, Masuda Y, Kimura G, Kawanami O, Masugi Y: The role of intraalveolar fibrosis in the process of pulmonary structural remodeling in patients with diffuse alveolar damage. Am J Pathol 1987, 126: 171–182
24. Kuhn C, McDonald JA: The roles of the myofibroblasts in idiopathic pulmonary fibrosis: ultrastructural and immunohistochemical features of sites of active extracel-

lular matrix synthesis. Am J Pathol 1991, 138:1257–1265
25. Kuhn C, Boldt J, King TE, Couch E, Vartio T, McDonald JA: An immunohistochemical study of architectural remodeling and connective tissue synthesis in pulmonary fibrosis. Am Rev Respir Dis 1989, 140: 1693–1703
26. Linder V, Reidy MA: Platelet-derived growth factor ligand and receptor expression by large vessel endothelium *in vivo*. Am J Pathol 1995, 146:1488–1497
27. Reidy MA, Fingerle J, Linder V: Factors controlling the development of arterial lesions after injury. Circulation 1992, 86(suppl III):43–46
28. Majesky MW, Giachelli CM, Reidy MA, Schwartz SM: Rat carotid neointimal smooth muscle cells reexpress a developmentally regulated mRNA phenotype during repair of arterial injury. Circ Res 1992, 71:759–768
29. Linder V, Giachelli CM, Schwartz SM, Reidy MA: A subpopulation of smooth muscle cells in injured rat arteries expresses platelet-derived growth factor-B chain mRNA. Circ Res 1995, 76:951–957
30. Amento EP, Ehasani N, Palmer H, Libby P: Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. Arterioscler Thromb 1991, 11: 1223–1230
31. Majesky MW, Reidy MA, Bowen-Pope DF, Hart CE, Wilcox JN, Schwartz SM: PDGF ligand and receptor gene expression during repair of arterial injury. J Cell Biol 1990, 111:2149–2158
32. Fingerle J, Au YPT, Clowes AW, Reidy MA: Intimal lesion formation in rat carotid arteries after endothelial denudation in absence of medial injury. Arteriosclerosis 1990, 10:1082–1087
33. Ferns GAA, Raines EW, Sprugel KH, Motani AS, Reidy MA, Ross R: Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. Science 1991, 253:1129–1132
34. Sundberg C, Ljungstrom M, Lindmark G, Gerdin B, Rubin K: Microvascular pericytes express platelet-derived growth factor-β receptors in human healing wounds and colorectal adenocarcinoma. Am J Pathol 1993, 143:1377–1388