PERGAMON The International Journal of Biochemistry & Cell Biology 34 (2002) 1534–1538

IJBCB

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Molecules in focus

Idiopathic pulmonary fibrosis: new insights in its pathogenesis

Annie Pardo [a,*], Moisés Selman [b,1]

[a] *Facultad de Ciencias, Universidad Nacional Autónoma de México, Apartado Postal 21-630, Coyoacan, México DF 04000, Mexico*
[b] *Instituto Nacional de Enfermedades Respiratorias, Tlalpan 4502, México DF 14080, Mexico*

Received 26 March 2002; received in revised form 6 June 2002; accepted 6 June 2002

Abstract

Idiopathic pulmonary fibrosis (IPF) is a unique type of chronic fibrosing lung disease of unknown etiology. The sequence of the pathogenic mechanisms is unknown, but the disease is characterized by epithelial injury and activation, the formation of distinctive subepithelial fibroblast/myofibroblast foci, and excessive extracellular matrix accumulation. These pathological processes usually lead to progressive and irreversible changes in the lung architecture resulting in progressive respiratory insufficiency and an almost universally terminal outcome in a relatively short period of time. While research has largely focused on inflammatory mechanisms for initiating the fibrotic response, recent evidence strongly suggests that disruption of the alveolar epithelium is an underlying pathogenic event. Although treatment to date has proved largely ineffective, this new approach has opened up several promising therapeutic avenues.
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Keywords: Idiopathic pulmonary fibrosis; Interstitial lung disease; Myofibroblast

1. Introduction

Pulmonary fibrosis is the final common pathway of a diverse group of lung disorders known as interstitial lung diseases (ILD). Although ILD are different in a variety of features, they are grouped together because they share many clinical, radiographic and physiological characteristics. One of the most common and by far the most aggressive ILD is idiopathic pulmonary fibrosis (IPF), which represents a chronic, progressive and usually lethal lung disorder of unknown etiology.

IPF has been reported world-wide and does not have predilection by race or ethnicity. Patients with IPF are usually 50–70 years of age at presentation, and the incidence is estimated at 7–10 cases per 100,000 per year. The accurate diagnosis of IPF requires a compatible clinical history, the exclusion of other known causes of ILD (such as drug injuries, environmental exposures, or collagen vascular diseases) and a surgical lung biopsy showing the characteristic histopathologic picture known as usual interstitial pneumonia.

It is important to emphasize that while most of ILD patients present a heterogeneous clinical behavior, that is, may heal, improve, or evolve to fibrosis, IPF always progress to destruction of the lung parenchyma [1]. Accordingly, the challenge is to understand why most subacute/chronic diffuse inflammatory lung disorders often respond to therapy while this does not occur in IPF.

* Corresponding author. Tel.: +52-5-622-4824; fax: +52-5-622-4910.
E-mail addresses: aps@hp.fciencias.unam.mx (A. Pardo), mselman@conacyt.mx (M. Selman).
[1] Tel.: +52-5-665-0043; fax: +52-5-665-4623.

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PII: S1357-2725(02)00091-2

2. Is inflammation a *pathogenic mechanism* in the development of IPF?

For a long time it has been assumed that chronic alveolitis *precedes* the fibrotic response and plays a *major role* in IPF lung fibrogenesis. However, several lines of evidence suggest that inflammation is not an important pathogenic event in IPF. Evidence includes the presence of similar mild/moderate alveolitis either in early or late disease, and the lack of response to potent and long-term anti-inflammatory therapy [1]. Additionally, experimental models and some human diseases show that it is possible to have an inflammation-independent fibrosis.

In this context, two different routes for developing diffuse pulmonary fibrosis have been proposed (Fig. 1): (a) *the inflammatory pathway* represented by almost all the non-IPF ILD, where there is an early, clearly distinguishable phase of alveolitis, followed by a subsequent fibrotic phase, and (b) *the epithelial pathway*, represented by IPF [1].

2.1. The epithelial pathway: the forgotten mechanism in the pathogenesis of IPF

Although several studies performed in experimental models, mainly of acute lung injury, emphasized about the importance of the alveolar epithelium for normal repair [2,3], the prevailing hypothesis regarding IPF has been that the disease is due to a chronic unsolved inflammatory response, and in this context, the possible role of epithelium was largely neglected.

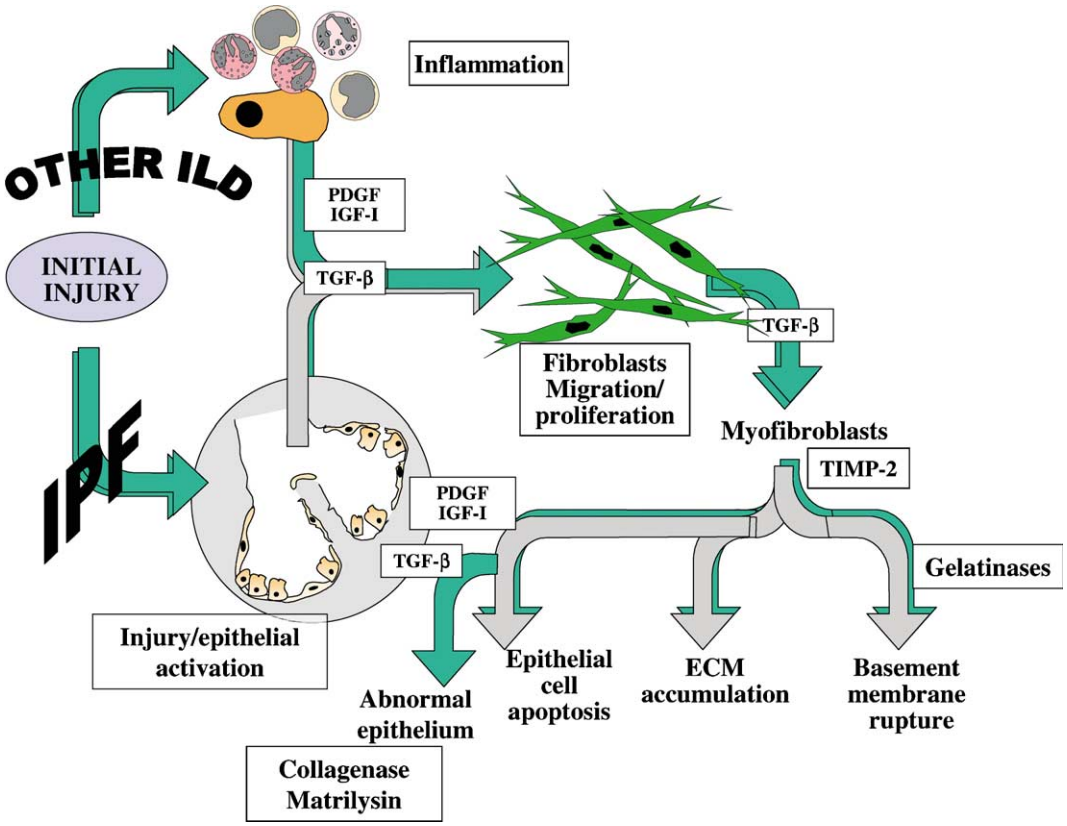

Fig. 1. Hypothetical scheme of the two pathways leading to lung fibrosis. An initial injury of known or unknown etiology provokes an unresolved inflammation or alveolar epithelial cell activation. Inflammatory and epithelial cells release cytokines/growth factors inducing fibroblast migration and proliferation and changes in cell phenotype (myofibroblasts). In the microenvironment of the injured lung, myofibroblasts may induce epithelial cell apoptosis, basement membrane disruption and aberrant extracellular matrix remodeling.

However, a marked disruption in the integrity of the alveolar epithelium with the presence of several altered phenotypes is a distinctive feature in any stage of IPF. In addition, numerous microscopic areas of alveolar epithelial cell dropout, often intercalated with hyperplastic cells, are usually noted mainly in areas of fibroblastic foci. In other words, an evident disarrangement in IPF lungs is a profound defect in the ability to conduct appropriate re-epithelialization. This pathological process together with the disruption of the epithelial basement membrane enhances the migration of fibroblasts into the alveolar spaces and the subsequent accumulation of intra-alveolar extracellular matrix.

In addition, numerous studies have demonstrated that activated alveolar epithelial cells in IPF lungs synthesize a variety of profibrotic molecules. For example, tissue factor and plasminogen activator inhibitor (PAI)-1 and (PAI)-2 may generate a procoagulant/anti-fibrinolytic intraalveolar environment facilitating an increased fibrotic response [4]. Thus, for example, experimental models of lung injury, such as that induced by nickel dust exposure, are characterized by PAI activation and fibrinolisis inhibition, and subsequently associated with excessive fibrin formation and strong fibrotic reaction [5].

Additionally, there is increasing evidence demonstrating that injured/activated alveolar epithelial cells express a variety of cytokines and growth factors involved in fibroblast migration, proliferation and phenotype changes, and in extracellular matrix remodeling. Studies approaching cell localization by immunohistochemistry and in situ hybridization have demonstrated that in IPF lungs, alveolar epithelial cells are the main site of synthesis of platelet-derived growth factor, transforming growth factor beta, tumor necrosis factor alpha, connective tissue growth factor, and endothelin-1, key actors in the development of pulmonary fibrosis [6–9]. Moreover, recent evidence strongly suggests that alveolar epithelium contributes in the generation of a Th2-like pattern of cytokine network in the lung microenvironment. Therefore, while in inflammatory ILD such as sarcoidosis and hypersensitivity pneumonitis type II pneumocytes express both interleukin-4 (IL-4) and interferon-γ (INF-γ), in IPF lungs only IL-4, a profibrotic cytokine, appears to be detectable [10].

All this data demonstrates that in IPF the alveolar epithelial cells rather than the inflammatory cells are the major players in the initiation of the fibrogenic events.

2.2. Myofibroblastic foci: starting the irreversible pathway to lung fibrotic destruction

An essential and distinctive morphological feature in IPF is the development of the so-called fibroblastic foci (Fig. 2), represented by widely scattered small aggregates of subepithelial fibroblasts and myofibroblasts immersed within a myxoid-appearing extracellular matrix. These mesenchymal cells represent foci of organizing acute lung injury and actively ongoing fibrogenic process and are characterized by spindle-shaped cells usually arranged with their long axis parallel to the long axis of the alveolar septa. The presence of these foci is followed by the abnormal remodeling of the ECM and the subsequent destruction of the lung architecture, and in this sense, they are considered as the key piece able to transform a potentially reversible disorder to a progressive and irreversible one. Actually, the amount of fibroblast/myofibroblast foci are considered a major prognostic factor in IPF patients [11]. However, the in vivo mechanisms leading to the activation of fibroblasts and the formation of foci of myofibroblasts in the injured lung parenchyma are still to be elucidated. By parallelism with skin wound healing we can assume that fibroblasts first take on a migratory phenotype, then a proliferative phenotype, and finally a myofibroblast profibrotic phenotype.

A critical issue is related to the persistence of the myofibroblasts in the fibroblastic foci. Normally, the resolution of normal wound healing includes a progressive decrease of myofibroblasts through apoptosis, and the question that arises is why this process does not seem to occur in IPF although IPF derived fibroblasts display an increased rate of spontaneous apoptosis in vitro [12]. The reason for this paradox is unknown, but it can be speculated that the cytokine/growth factor/matrix network in the IPF lung microenvironment facilitates myofibroblast survival in vivo. In this context, the notable expression of tissue inhibitors of metalloproteinase (TIMP-2) in the fibroblastic foci may be related to longer survival since in addition to its MMP inhibitory function it is also able to induce proliferation [13].

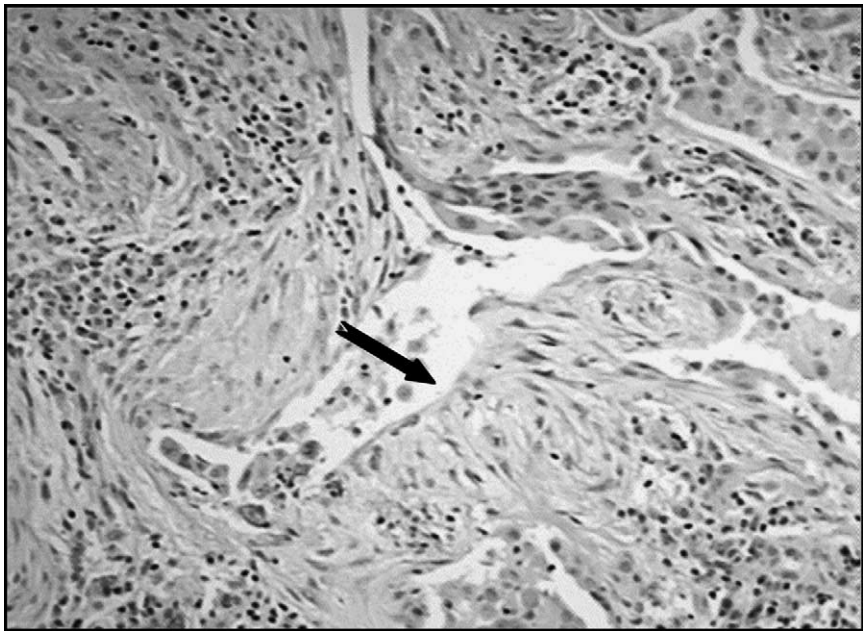

Fig. 2. Subepithelial fibroblastic foci in an IPF lung. It can be noticed there are a large area of alveolar epithelial cell loss (arrow).

2.3. Fibroblastic/myofibroblastic foci and lung fibrogenesis

The increase of myofibroblasts in injured lungs has several deleterious effects, contributing on one hand to the abnormal alveolar re-epithelialization, and on the other to the excessive and disordered deposition of extracellular matrix in the lung parenchyma.

Regarding the former, it has been demonstrated that IPF fibroblasts produce angiotensin peptides able to induce epithelial cell death in vitro, which also probably occurs in vivo [14,15]. In addition, IPF myofibroblasts synthesize gelatinases A and B, two matrix metalloproteinases that degrade basement membrane molecules, contributing to the failure of an orderly repair of alveolar type I epithelial cells and enhancing the migration of fibroblasts/myofibroblasts into the alveolar spaces [13].

2.4. Collagenases and lung fibrosis: location! . . . location!

The aberrant ECM remodeling is the final common feature of any fibrotic disorder, and some recent evidence suggests a pivotal role for some MMPs and their natural inhibitors, known as TIMPs [1,13]. Thus, in vivo studies have surprisingly demonstrated that interstitial collagenase (MMP-1), the enzyme that has been claimed to be responsible for the degradation of fibrillar collagens is highly upregulated in IPF lung tissue. However, it is primarily located in reactive alveolar epithelial cells as well as bronchiolar epithelial cells lining honeycomb cystic spaces, while interstitial fibroblasts and tissue scar seem to be virtually free of collagenases. By contrast, the four TIMPs are usually in interstitial localization where extracellular matrix is being accumulated. Moreover, in contrast to MMP-1, fibroblasts/myofibroblasts obtained from IPF lungs exhibited a marked upregulation of all four TIMPs as compared with fibroblasts from normal lungs [12]. Therefore, it seems that a non-degrading fibrillar collagen microenvironment is present in IPF lungs.

2.5. Therapy

At present, there is no effective drug therapy for IPF and the patients usually progress showing a fatal outcome in a few years. On the basis that IPF

is an inflammatory process that evolves to fibrosis, the natural choice for treatment has been the use of corticosteroids and other immunosuppressive drugs. However, there is no objective evidence of long-term improvement, and this treatment is associated with serious side effects. Therapies designed to inhibit fibroblast proliferation and ECM accumulation are now being evaluated. Two of these agents are pirfenidone, a novel anti-fibrotic drug found to reduce bleomycin induced lung fibrosis, and have some effects in human IPF, and interferon-γ which in a double-blind trial was demonstrated to induce a significant improvement in lung function and symptoms [16]. Larger confirmatory trials are now running and in the near future we will know how good these drugs are for IPF patients.

Another promising target is the alveolar epithelial cell that, as mentioned, plays a major role in the pathogenesis of IPF. Experimental evidence suggests that some epithelial proliferating agents such as keratinocyte growth factor or hepatocyte growth factor may ameliorate the tissue fibrotic response [1]. In this context, it is important to emphasize that probably no single agent is going to work in this disease and that a combination, including agents blocking fibroblasts and enhancing re-epithelialization, will be necessary. Improvement of our knowledge about the biopathological principles of the disease will increase the opportunities of finding new agents.

References

[1] M. Selman, T.E. King, A. Pardo, Idiopathic pulmonary fibrosis: Prevaling and evolving hypotheses about its pathogenesis and implications for therapy, Ann. Int. Med. 134 (2001) 136–151.

[2] I.Y.R. Adamson, L. Young, D.H. Bowden, Relationships of alveolar epithelial injury and repair to the induction of pulmonary fibrosis, Am. J. Pathol. 130 (1988) 377–383.

[3] W.M. Haschek, H.P. Witschi, Pulmonary fibrosis: a possible mechanism, Toxicol. Appl. Pharmacol. 51 (1979) 475–487.

[4] S. Imokawa, A. Sato, H. Hayakawa, M. Kotani, T. Urano, A. Takada, Tissue factor expression and fibrin deposition in the lungs of patients with idiopathic pulmonary fibrosis and systemic sclerosis, Am. J. Respir. Crit. Care Med. 156 (1997) 631–636.

[5] A.S. Andrew, L.R. Klei, A. Barchowsky, AP-1-dependent induction of plasminogen activator inhibitor-1 by nickel does not require reactive oxygen, Am. J. Physiol. Lung Cell. Mol. Physiol. 281 (2001) L616–L623.

[6] H.N. Antoniades, M.A. Bravo, R.E. Avila, T. Galanopoulus, J. Neville, M. Selman, Platelet-derived growth factor in idiopathic pulmonary fibrosis, J. Clin. Invest. 86 (1990) 1055–1064.

[7] Y. Kapanci, A. Desmouliere, J.C. Pache, M. Redard, G. Gabbiani, Cytoskeletal protein modulation in pulmonary alveolar myofibroblasts during idiopathic pulmonary fibrosis. Possible role of transforming growth factor beta and tumor necrosis factor alpha., Am. J. Respir. Crit. Care Med. 152 (1995) 2163–2169.

[8] A. Giaid, R.P. Michel, D.J. Stewart, M. Sheppard, B. Corrin, Q. Hamid, Expression of endothelin-1 in lung of patients with cryptogenic fibrosing alveolitis, Lancet 341 (1993) 1550–1554.

[9] L.H. Pan, K. Yamauchi, M. Uzuki, T. Nakanishi, M. Takigawa, H. Inoue, T. Sawai, Type II alveolar epithelial cells and interstitial fibroblasts express connective tissue growth factor in IPF, Eur. Respir. J. 17 (2001) 1220–1227.

[10] W.A. Wallace, S.E. Howie, Immunoreactive interleukin-4 and interferon-γ expression by type II alveolar epithelial cells in interstitial lung disease, J. Pathol. 187 (1999) 475–480.

[11] T.E. King Jr., M.I. Schwarz, K. Brown, J.A. Tooze, T.V. Colby, J.A. Waldron Jr., A. Flint, W. Thurlbeck, R.M. Cherniack, Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality, Am. J. Respir. Crit. Care Med. 164 (2001) 1025–1032.

[12] C. Ramos, M. Montaño, J. García-Alvarez, V. Ruiz, B.D. Uhal, M. Selman, A. Pardo, Fibroblasts from idiopathic pulmonary fibrosis and normal lungs differ in growth rate, apoptosis, and TIMP's expression, Am. J. Respir. Cell Mol. Biol. 24 (2001) 591–598.

[13] M. Selman, V. Ruiz, S. Cabrera, L. Segura, R. Ramírez, R. Barrios, A. Pardo, TIMP-1, -2, -3 and -4 in idiopathic pulmonary fibrosis. A prevailing non degradative lung microenvironment? Am. J. Physiol. 279 (2000) L562–L574.

[14] B.D. Uhal, I. Joshi, A.L. True, S. Mundle, A. Raza, A. Pardo, M. Selman, Fibroblasts isolated after fibrotic lung injury induce apoptosis of alveolar epithelial cells in vitro, Am. J. Physiol. 269 (1995) L819–828.

[15] B.D. Uhal, I. Joshi, W.F. Hughes, C. Ramos, A. Pardo, M. Selman, Alveolar epithelial cell death adjacent to underlying myofibroblasts in advanced fibrotic human lung, Am. J. Physiol. 275 (1998) L1192–L1199.

[16] T.J. Gross, G.W. Hunninghake, Idiopathic pulmonary fibrosis, N. Engl. J. Med. 345 (2001) 517–525.