Review Article

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Physiopathological Mechanisms Involved in the Progression of Pulmonary Fibrosis: A Systematic Review

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Idiopathic Pulmonary Fibrosis (IPF) is a lung disease characterized by formation of fibroblast foci and honeycomb lesions in the pulmonary parenchyma. The physiopathological mechanisms involved in the development of fibrosis and architectural disorganization are still imperfectly elucidated. In fact, lesion formation is irreversible and no treatment, to date, has been shown to be effective (30% of patients die within 5 years of the onset of the disease). The long-held concept of chronic inflammation leading to fibrosis is still controversial. Indeed, recent data suggest that the physiopathology of this disease is the product of fibroblast dysfunction rather than the result of an inflammatory imbalance. This concept supports the parallel involvement of three main factors: epithelial damage, angiogenesis and oxidative stress. In this review we highlighted the different factors and the ethiopathogenic pathways involved in the fibrotic process, in order to increase our understanding of the mechanisms involved in this pulmonary pathology.

Key words: Fibroblasts; Inflammation; Epithelial damage; Angiogenesis; Oxidative stress

Idiopathic Pulmonary Fibrosis (IPF)

IPF is the most common and severe disease of diffuse interstitial pneumonia, mainly affecting the lung connective tissue (1). The connective tissue surrounding the alveoli becomes thick and rigid, altering pulmonary distensibility and thus alveolar-capillary diffusion of O_2 and CO_2. These disturbances in respiratory mechanics and gas exchange inevitably lead to respiratory insufficiency (2).

Nowadays, despite the progress in clinical and basic research, the pathogenesis of IPF is still poorly understood and available drug treatments have limited efficacy and significant side effects (3-5). It is currently admitted that chronic inflammation is not the major factor responsible for fibrosis, since fibroblastic proliferation causing aberrant healing and accumulation of extracellular matrix (ECM) proteins such as collagen is also recorded (6,7).

The natural history of IPF is variable and unpredictable from patient to patient. Some patients undergo long periods of stability, while others suffer from frequent exacerbations (8). IPF mostly affects the aged people, with a median survival of 3 to 5 years after disease diagnosis (9). IPF is a lung pathology of unknown etiology, although risk factors such as smoking and other environmental exposures have been described. Genetic transmission is also involved (6). However, it is rare and does not exceed 3% of cases.

Physiopathology of IPF

IPF is a heterogeneous process where inflammation is considered as one of the etiopathogenic pathways (10). The fibrotic parenchyma is characterized by the presence of multiple fibroblastic foci which result in the destruction of

the parenchyma. This disease has multifactorial origin involving epithelial damage, vascular abnormalities, inflammation, oxidative stress and pulmonary aging (11).

Fibroblasts: cells most involved?

Definition

Fibrosis is closely related to the proliferation of fibroblasts (Figure 1). These cells excessively secrete ECM and collagen during their proliferation, which leads to functional impairment and permanent scar formation (12).

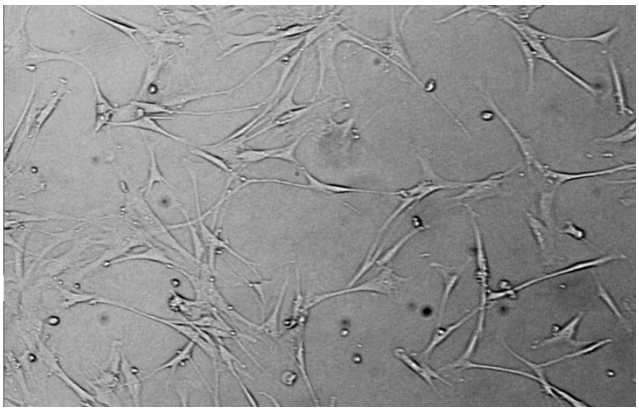

Figure 1. Human pulmonary fibroblasts (HLF) observed under optical microscope (Magnification x 5).

Role of fibroblasts in the ECM maintenance and production

Fibroblasts synthesize extracellular matrix components including structural proteins. These cells express many subtypes of collagen and elastin, allowing tissues to acquire different degrees of rigidity and / or flexibility (13). Fibroblasts assure also fibronectin and laminin expression. These proteins ensure cells and ECM association and can interact with some transmembrane adhesion protein such as integrin, allowing them to be a good candidate as biomarkers for hepatic fibrosis (14,15).

The fundamental substance of ECM provides a final pathway for the flow of nutrients to tissues, an intercellular communication pathway, and a pathway for the migration of immune cells, fibroblasts and myofibroblasts. It is also an essential route for the migration of endothelial cells during angiogenesis (16).

Fibroblasts also produce ECM degradation enzymes (such as metalloproteinases or MMPs) and their inhibitors (tissue metalloproteinase inhibitors or TIMPs). Therefore, they are responsible for the maintenance and degradation of ECM and are also believed to be involved in inflammation, angiogenesis and cancer progression. These cells produce and respond to a wide range of autocrine and paracrine signals, such as cytokines and growth factors. Thus, targeting of some auxiliary signaling molecules could contribute to the discovery of new drugs for therapeutic purposes (16).

Etiopathogenic mechanisms of IPF

Epithelial lesions

Several environmental and genetic factors have been described in the development of IPF. These factors act by exerting an increased stress on the endoplasmic reticulum of epithelial cells and consequently induce their destruction and apoptosis. Thus, we have noticed that the number of type I pneumocytes, the major cells of the alveolar epithelial surface, is greatly reduced in advanced IPF (17). These epithelial abnormalities are accompanied by a release of growth / profibrotic factors such as TGF-β, TNF-α and PDGF, which participate in the proliferation of fibroblasts and their differentiation into myofibroblasts (18).

Fibrosis pathogenesis is ensured, among others, by fibroblasts and myofibroblasts accumulation (19). This process is insured by mesenchymal cells expansion, epithelial-mesenchymal transition (EMT), and fibrocytes differentiation (20).

This accumulation causes the appearance of fibroblast foci around alveolar epithelium, while intra-alveolar and interstitial myofibroblasts release some apoptotic factors inducing impairment in alveolar re-epithelialization capacity. Myofibroblasts possess a great profibrotic potential and synthesize collagen in excess in the ECM leading to pulmonary architecture destruction. Finally, the accumulation of fibroblasts and myofibroblasts is favored by their excessive proliferation and the decrease in their apoptosis (8) (Figure 2).

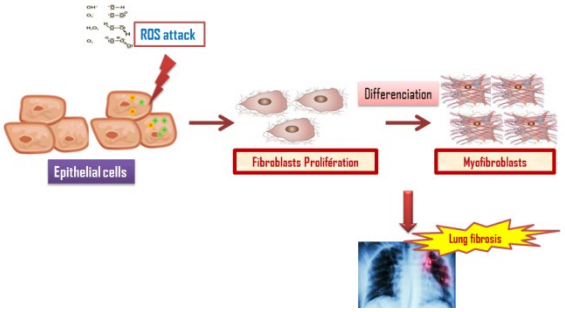

Figure 2. Pulmonary fibrosis. Oxidative stress can cause increased reactive oxygen species inducing alveolar epithelial cells damage. These cells secrete growth factors which promote the proliferation of fibroblasts and their differentiation into myofibroblasts leading to pulmonary fibrosis.

Metalloproteases (MPP) are collagenases involved primarily in the degradation of ECM (21). Fibroblasts and myofibroblasts play an essential role in the synthesis, deposition and remodeling of ECM. The result is a pulmonary architectural disorganization associated with a profound modification of the microenvironment and cellular interactions (22). Fibroblasts of the fibrotic lung intensely express 4 types of MPP inhibitors called TIMPs or "Tissue inhibitor of metalloproteinase " (23), which leads to an imbalance between MMPs and TIMPs level, in favor of TIMP and explains the decrease in collagen degradation in the damaged parenchyma (24, 25).

Inflammation

Inflammation was usually considered to be one of the mechanisms behind pulmonary fibrosis and has been shown to play a significant role in the fibrotic process. However, not all forms of fibrosis are inflammatory in origin. Indeed, IPF can be secondary to exposure to some environmental factors in genetically susceptible people. Inflammatory reaction in these patients is often exaggerated and is characterized by an accumulation of leukocytes in the plasma and alveoli, causing impaired gas exchange.

Inflammation in IPF patients

In humans, fibrotic lungs contain a variety of immune cell population involving macrophages, neutrophils, eosinophils and lymphocytes. The simultaneous release of cytokines and growth factors amplifies this process (26) (Figure 3). It is also interesting to note that "type of cytokine" can orient towards the predominant cell type during the critical stages of the disease such as interleukins IL4, IL5 and IL13 produced by LTCD4 or Th2 (27).

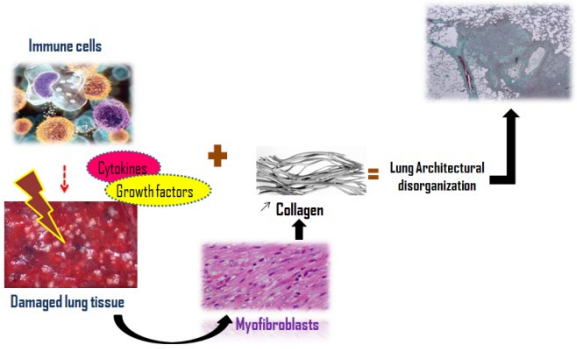

Figure 3. Inflammation and fibrosis. The simultaneous release of cytokines and growth factors by the immune cells amplifies the fibrotic process by inducing pulmonary cells lesions. Collagen release by myofibroblasts is also implicated so both of these mechanisms induce an architectural disorganization of the lung.

Involvement of cytokines and growth factors

TGF β

Studies of pulmonary and hepatic fibrosis models have demonstrated the central role of TGF- β (28). Indeed, in some pathologies, particularly fibrosis, the overexpression of this cytokine in its active form is particularly associated with increased expression of collagen in the same territory where the ECM is accumulated. In addition, TGF-β lung level is increased in the lungs of patients with pulmonary fibrosis, especially in the areas of regeneration and remodeling (28). It is currently accepted that TGF-β is one of the best known profibrotic mediators that constitutes an essential therapeutic target in the treatment of IPF (29) (Figure 4).

Connective tissue growth factor (CTGF)

CTGF (also called CCN2) is a member of the CCN family of growth factors (Ctgf, Cyr61 / cef 10 and Nov) which play a modulating role (stimulator or inhibitor) of growth in various biological processes (30).

Several studies have shown that CTGF activity is selectively induced by TGF-β (31,32). These two proteins

are specially expressed in tissue repair and fibrotic areas. CTGF acts as a secondary cytokine compared to TGF-β, but is thought to potentiate the profibrotic activity of TGF-β (31).

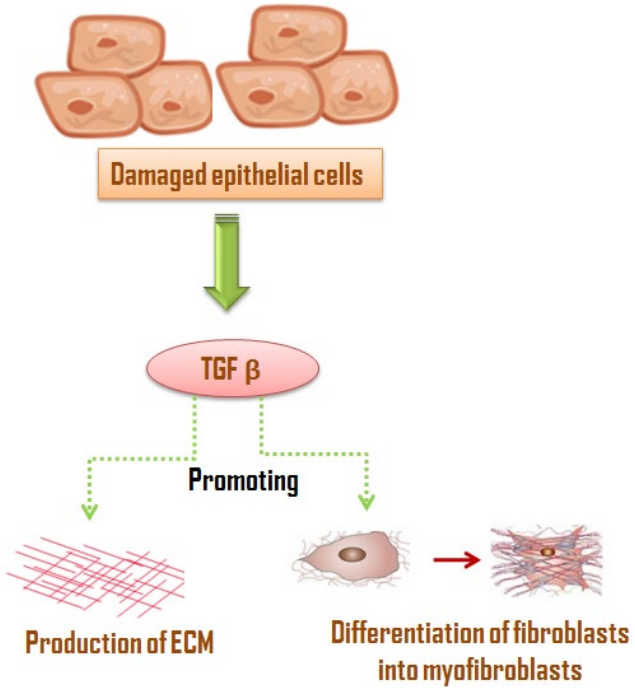

Figure 4. Involvement of TGF-β in fibrosis. During the fibrotic process, alveolar epithelial cells secrete high amount of TGF-β, which promotes ECM production and the differentiation of fibroblasts into myofibroblasts.

Epithelial-mesenchymal transition (EMT)

According to Thannickal et al. (33), fibroblasts isolated from lungs of patients with IPF have heterogeneous phenotypes and properties, different from those of normal lung fibroblasts. This heterogeneity is explained by the fact that fibroblasts are derived from several types of cells, particularly following an EMT.

EMT is one of the cellular processes that lead to the accumulation of fibroblasts and myofibroblasts in the lungs of patients with IPF from epithelial cells (34). These cells lose their initial phenotype and acquire that of mesenchymal cells. EMT involving resident epithelial cells is thought to occur in response to injury, which protects them from cell death and provides an additional source of fibroblasts needed to repair damaged tissues (32). This mechanism involves several intracellular signaling pathways including Smads and integrins.

EMT also involves several mediators such as EGF (Epidermal Growth Factor), HGF (Hepatocyte Growth Factor), FGF (Fibroblast Growth Factor), ECM components (mainly collagen) as well as TGFβ-1 (35).

Finally, it should be noted that type II pneumocytes can also undergo an EMT towards fibroblasts and myofibroblasts, under specific conditions when this transition is inhibited for type I pneumocytes.

Oxidative stress

Recent studies suggest that oxidative stress play an important role in the pathogenesis of fibrosis (36).

Generation of Mitochondrial reactive oxygen species (ROS) has been shown to be associated with increased cellular oxidative stress in lung (36). This stress can lead directly to the damage, activation and / or apoptosis of alveolar epithelial cells, by disturbing the intracellular redox balance or indirectly, by activating some signaling pathways, such as transcription factors and angiotensin converting enzyme, considered to mediate oxidative stress (37). We noticed also NADPH oxidase (NOX) generation by ROS, including NOX1 (38), NOX2 (39) and NOX4 (40), thus contributing to tissue fibrosis. On the other hand, previous work detected higher levels of 8-isoprostane, an oxidative stress biomarker in the bronchoalveolar lavage fluid of patients with IPF than that of control subjects (41).

Other studies indicate that ECM is also affected by the oxidative stress in the lungs of patients affected by IPF. In fact, ECM is an essential element in the regulation of cell homeostasis and healing, and the degraded products of this matrix, released following ROS attack generated by oxidative stress, promote fibrogenesis and modulate the activity of epithelial, mesenchymal and inflammatory cells. Therefore, interactions between oxidative stress and ECM may be an important target for new therapies in IPF (42).

Angiogenesis and vascular remodeling

Some research works reported that IPF is associated with an increase of angiogenesis, but these results are controversial according to recent studies which rather report the reduction of angiogenesis in fibrotic lungs (43). Indeed, the suppression of angiogenesis in fibroblast foci seems to be linked to a local imbalance between angiogenic (VEGF or vascular endothelial growth factor) and angiostatic (PEDF or Pigment Epithelium-Derived Factor) mediators.

Antoniou et al. (44) showed that the level of angiogenic chemokines such as "Growth-Related Gene-Alpha", "Epithelial Neutrophil-Activating Protein–78" and ''interleukin-8'' is significantly increased in the bronchoalveolar fluid of patients with IPF compared to healthy subjects. In contrast, angiostatic chemokines remained at normal levels. These results diminished the possibility of tissue repair and promote the proliferation of fibroblasts in IPF, at the time when non-fibrotic tissues are characterized by abundant neovascularization showing abnormal vascular remodeling (45).

Current therapeutic data

In October 2014, Pirfenidone and Nintedanib were officially recognized by the FDA or "US Food and Drug Administration".

Pirfenidone (5-methyl-1-phenyl-2- [1H] pyridone) has antioxidant, anti-inflammatory and antifibrotic effects, while nintedanib is an intracellular inhibitor of tyrosine kinases, including receptors for growth factor fibroblasts (FGF), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) (18). These drugs reduce the risk of death of IPF patients (46). However, these two drugs are unable to reduce the risk of acute exacerbation as well as disease aggravation (4,47).

Lung transplantation remains the best alternative which can significantly improve patients' quality of life and can extend their life expectancy by several years by reducing the risk of death by up to 75% (48).

Research on IPF is therefore, continuing with two fundamental objectives: to fully understand the mechanisms that lead to pulmonary fibrosis and thus to improve treatment (49).

The beneficial effects of plant extracts in the treatment of IPF have been reported by several research teams around the world (50,51). These extracts are able to modulate various fibrotic markers (such as collagen, hydroxyproline, MMPs, ...), inflammatory biomarkers (TGF-α, TGF-β, interleukins, …) as well as the activity of antioxidant enzymes (Superoxide dismutase, catalase, ...) and the attenuation of ROS generation via the activation of multiple signaling pathways, in order to ensure the inhibition of pulmonary fibrosis.

Plant extracts application can inhibit pulmonary fibrosis by modulating the activity and expression of various markers linked to this disease. In particular, many plant extracts rich with phenolic compounds have been tested by our team research for the treatment of experimental pulmonary fibrosis induced by bleomycin in wistar rats (52-58). Each plant extract used was able to activate several ethiopathogenic pathways to exert its curative effect against experimental fibrosis induced by bleomycin. These extracts are promising candidates that may offer a new therapeutic alternative in the treatment of pulmonary fibrosis.

CONCLUSION

Current treatments prescribed for the treatment of IPF are partially effective and can induce varying degrees of side effects. The discovery of a therapeutic agent which would block several ethiopathogenic pathways, becomes the major objective of research teams in this field. Plant extracts and bioactive molecule approach can contribute to the opening of new therapeutic pathways in the field of

pulmonary fibrosis, for which no therapeutic combination has proved to be effective today.

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