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REVIEW

Cellular Mechanisms in the Pathogenesis of Idiopathic Pulmonary Fibrosis

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ABSTRACT

Current evidence suggests that the fibrotic response in idiopathic pulmonary fibrosis (IPF) arises due to accelerated aging of the lung after repeated injuries to the alveolar epithelium, which causes the production of inflammatory mediators that induce the recruitment and activation of lung fibroblasts. These cells are responsible for the secretion of excessive amounts of collagen fibers, destroying the normal lung architecture leading to decreased lung compliance, disrupted gas exchange, and, ultimately, respiratory failure.

Different alterations of cellular function have been proposed to be related to the premature aging of pulmonary tissue in IPF, such as defects in DNA repair, mitochondrial dysfunction, telomeric shortening, loss of protein homeostasis, and cellular senescence.

Improving our understanding of the pathophysiology of this disease is a crucial point to find new therapeutic targets. In the following article, we review recent data on the underlying mechanisms thought to be involved in the pathogenesis of IPF. **(BRN Rev. 2021;7(2):82-95)**

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease that develops, maybe in part, due to different cellular processes that cause a progressive increase in the aging of the lung tissue.

IPF prevalence is currently increasing, with Europe and North America being the regions with the highest rate: up to 3 to 9 cases per 100.000 persons-year[1]. Unfortunately, IPF patients have a poor prognosis since it has an average survival rate of 3.8 years among adults over 65 in the USA[2]. In recent years, the treatment of IPF has undergone substantial improvement due to the antifibrotic drugs pirfenidone and nintedanib, which have demonstrated in clinical trials their ability to decrease the functional deterioration with a slight improvement in the survival of patients with IPF. However, the destruction of the pulmonary parenchyma that causes the disease is not reversible, making pulmonary transplantation the only therapy for patients with IPF.

Understanding the different pathophysiological mechanisms involved at the cellular level in the development of IPF is essential to improve our knowledge of the disease, assess the prognosis of patients, and advance in the development of new curative therapies.

In this manuscript, we will review the cellular processes involved in lung aging in IPF, such as telomeric shortening, loss of proteostasis, mitochondrial dysfunction, or loss of repair capacity of mesenchymal progenitor cells. All this will contribute to the loss of correct function of the different cellular subpopulations in the lung parenchyma.

ROLE OF LUNG CELLS IN FIBROSIS

The histopathological characteristics of IPF include the abnormal increase of mesenchymal cells, dysmorphic epithelial cells, overproduction and disorganized collagen deposits in the extracellular matrix, distortion of the pulmonary architecture with the appearance of cystic spaces (honeycombing), as well as foci with accumulations of fibroblasts, which are characteristic of the usual interstitial pneumonia (UIP) pattern of IPF[3-7].

In animal models, using bleomycin instillation into the lung, pathogenesis of the pulmonary fibrosis shows a predominantly inflammatory cellular pattern formed by cells such as alveolar macrophages, eosinophils, neutrophils, and lymphocytes in response to tissue damage[8-9]. It has been proposed that alveolar macrophages could play a fundamental role given their ability to secrete proinflammatory molecules and profibrotic cytokines that would target the mesenchymal cells promoting collagen deposits[4,10].

These findings, and recent data from single-cell RNA seq studies, had contributed to defining the current theory on the pathogenesis of IPF because its origin comes from the interaction of aberrant fibroblasts, epithelial cells, and activated macrophages. This explanation is supported by the presence of fibroblastic foci in areas with altered basal membrane directly below the areas with damaged epithelium without the presence of a significant inflammatory cellular infiltrate[11-13]. All this would lead to a progressive accumulation of extracellular matrix proteins that would damage the lung tissue structure and progressive fibrosis.

Table 1. Summary of cellular mechanisms involved in pathogenesis of IPF

Cellular mechanisms
1. Alveolar epithelium cells: – Changes in regular composition of alveolar epithelium: loss of pneumocytes type I which entails and impaired gas exchange through alveolar capillary membrane and proliferation of pneumocytes type II with lack of normal reepithelialization after a lung injury. – Release of growth factors and cytokines after repeated microlesions to epithelial cells: transforming growth factor (TGF-B1), connective tissue growth factor (CTGF), fibroblast growth factor (FGF-2) and interleukins (ILs) among them.
2. Fibroblast and myofibroblast: – Recruitment and proliferation. Fibroblast foci. – Increased production of collagen fibers with a decrease in its degradation producing an abnormal deposit of collagen in the extracellular tissue.
3. Mesenquimal stem cells: – Decrease in their capacity of cellular regeneration due to the loss of their reparative capacities.

The main cell types that intervene in the etiology of IPF are described in the following sections (Table 1).

Role of epithelial cells in IPF

Although the precise agents that initiate the changes observed in IPF are still unknown, a series of factors that could contribute to the development and perpetuation of the fibrotic response have been identified, among which are: predisposing genetic factors (mutations of surfactant proteins, MUC5B mutations, and telomeric shortening)[4,14-28], external triggers (tobacco, viral infections, environmental contaminants, chronic microaspiration, and drug toxicity)[29] as well as a dysregulation between oxidant and antioxidant factors and an imbalance between cell-derived cytokines Th1 and Th2[30-33].

It has been proposed that repeated subclinical lesions in the lung cause damage to the alveolar epithelium, subepithelial region, and basal endothelial membrane. This lesion allows entry into the alveolus of exudate with a high concentration of pro-inflammatory cytokines formed by cells of the mesenchymal lineage. The organization of the exudate leads to alveolar collapse, the juxtaposition of denuded alveolar walls, and the loss of surfactant[34]. Both the epithelial lesion and the basal membrane appear to be necessary for the development of intraluminal fibrosis.

In the normal lung, the alveolar epithelium comprises type I epithelial cells, with a relatively small number of type II epithelial cells[35]. Type I epithelial cells cover 90% of the alveolar surface and are responsible for performing the exchange of gases through the alveolar-capillary membrane. On the other hand, type II epithelial cells have a role in the synthesis and secretion of surfactant, a compound formed by proteins and phospholipids that significantly reduces the surface tension inside the pulmonary alveoli, preventing its collapse. In a normal situation, type II epithelial cells are also responsible after an injury for the re-epithelialization of damaged alveoli[36] restoring the numbers of type I and type II cells. However, in IPF, a loss of type I epithelial cells and a reduced reparative capacity of type II cells are observed. This lack of normal re-epithelialization could be due, in part, to aberrant activation of Wnt proteins after a lung injury. These proteins would inhibit the phosphorylation of beta-catenin by glycogen synthase kinase 3b (GSK3b), preventing its translocation to the nucleus and activating the lymphoid enhancing factor/T-cell factor (LEF / TCF); this pathway would be involved in the

activation of proliferation and absence of differentiation of type II cells[37].

Data from single RNA sequence analysis of the IPF lungs have demonstrated a new basaloid epithelial cell that localizes in the IPF foci. In addition, these cells express markers of basal cells, cytokeratin 17, and are senescent. Thus, suggesting that these cells may be the ones trigging the aberrant interaction of epithelial cells and mesenchymal cells.

After the initial injury to these epithelial cells, the release of a series of growth factors and cytokines occurs. Among them, it is worth highlighting the transforming growth factor-beta (TGF-ß1)[38-39], which is one of the most potent regulators of connective tissue synthesis, increasing its production and inhibiting its proteases[38-40]. However, it can also induce other growth factors and cytokines involved in fibrosis, including connective tissue growth factor (CTGF), fibroblast growth factor (FGF-2), platelet-derived growth factor (PDGF), the insulin-like growth factor (IGF), and interleukins (ILs)[41-42]. Recent clinical studies support the role of TGF-ß1 in the pathogenesis of IPF, having demonstrated the inhibition of fibrosis in experimental animals by reducing their expression, signaling, and activity.

Another cytokine involved in IPF is the tumor necrosis factor (TNF-α), whose expression is increased in IPF, increasing the production of TGF-ß1 as well as stimulate the proliferation of fibroblasts and induce the synthesis of collagen[43-44].

There is also overexpression of fibrotic cytokines, including monocyte chemoattractant protein 1 (MCP-1), IL-4, IL-13, FGF-2, IGF-1, PDGF, and GM-CSF. All these mediators would be involved in the activation and recruitment of circulating fibrocytes, thus perpetuating the response to cell damage.

Despite the role of inflammation in IPF pathogenesis being controversial, new insight provides evidence of the role of certain cell types that are activated in response to the release of chemokines and interleukines[45] such as neutrophils (a major player in the acute phase of lung damage, which accumulation could lead to tissue remodeling and fibrosis), macrophages (they may exhibit anti-fibrotic and pro-fibrotic tissue regeneration functions, which depends on the cytokine environment, M2 macrophages appear to have a special role in the regulation of fibrosis being involved in acute exacerbations), fibrocytes (which contribute to fibroblast activation and production of extracellular matrix), type 2 innate lymphoid cells (that contribute to inflammatory responses and extracellular matrix homeostasis by releasing a wide array of mediators) and adaptive immune system (Th1 and Th2 cells involved with attenuation of fibrosis and activation of fibroblast respectively and B-cells whose concentration along with total immunoglobulins correlates with disease outcome).

The role of fibroblasts in IPF

The cytokines and growth factors secreted in response to repeated microlesions to epithelial cells result in the recruitment of fibroblasts derived from different sources: lung interstitial, peribranchial, pericytes, and mesenchymal stem cells.

Subpopulations of fibroblasts in patients with IPF show some significant differences compared to isolated fibroblasts in normal lungs. These differences include increased cellular senescence with higher expression of ß-galactosidase, p21, p16, p53 and cytokines related to the senescence-associated secretory phenotype (SASP) as well as decreased proliferation/apoptosis compared to normal controls. Additionally, in a recent study[46] it was observed that shorter telomeres, mitochondrial dysfunction and upon transforming growth factor- ß stimulation increased markers of endoplasmic reticulum stress.

Fibroblast-derived myofibroblasts are cells that express characteristics of fibroblasts and smooth muscle cells and are identified by their expression of smooth muscle alpha actin (AMS)[47]. After being recruited or differentiated from lung resident fibroblasts, both types of cells are organized in fibrotic foci, these being the histological characteristics of the UIP[3,7]. These foci of fibroblasts and myofibroblasts are located adjacent to areas of epithelial damage and of the basal membrane and precede the onset of advanced stage fibrosis. Myofibroblasts produce interstitial collagen in significantly greater amounts than fibroblasts[48-49], leading to their accumulation in the extracellular matrix of the lung. Collagen type III is the predominant form of collagen in areas of initial fibrosis, while type I collagen predominates in areas of mature fibrosis.

In normal lungs, collagen is produced and continuously degraded by a family of matrix metalloproteinases (MMPs) that include collagenases[50] secreted by fibroblasts, epithelial cells, neutrophils and macrophages; this process is tightly regulated to preserve the normal structure of the lung.

In patients with IPF, there is an imbalance between the interstitial collagenases and their tissue inhibitors. The increased synthesis of collagen accompanied by a decrease in its degradation would cause an abnormal deposition of collagen in the extracellular tissue.

The progressive deposit of extracellular matrix leads to a distorted pulmonary architecture with loss of capillary surface area and dysfunction of gas exchange units, and the fibrotic lung with resultant honeycombing areas has no potential capacity for regeneration and repair of lesions.

Alteration on lung repair in IPF lungs

In addition to the defects on type II epithelial cells, in IPF, there is a decrease in the capacity of cellular auto regeneration by mesenchymal progenitor cells due to the loss of their reparative capacities[51], producing an imbalance between the rate of cellular renewal and differentiation[52].

In IPF, the alteration of repair capacity and a distorted epithelial-mesenchymal communication produces a proliferation of abnormal bronchial epithelium and the lesion and hyperplasia of alveolar epithelial cells, particularly the phenotypic changes of the alveolar type cells II[53].

In addition, mesenchymal cells in IPF show signs of senescence with increased p21 marker expression, shorter telomere length, longer

duplication times, and changes in mitochondrial function and morphology (decrease in size, decreased oxygen consumption, and decreased glycolysis capacity). All this makes the mesenchymal cells less functional, as could be confirmed in studies based on the induction of fibrotic lung injury in mice with bleomycin, showing a less effective tissue repair by progenitor cells in sick subjects compared to healthy ones[54].

Mesenchymal progenitor cells have been suggested as potentially therapeutic for patients with IPF due to their role in tissue repair and wound healing combined with their immunomodulatory properties[55-56]. It is known that these cells produce soluble factors such as fibronectin, periostin, lumican, and insulin-like growth factor-binding protein 7 (IGFBP7) that are involved in epithelial repairment. In addition, it has been shown in studies in mice with bleomycin-induced pulmonary fibrosis that mesenchymal cells exert a protective effect by improving inflammation and reducing the degree of injury and fibrosis[57]. This would lead to the conclusion that the implant of healthy mesenchymal progenitor cells could play a role in the future treatment of IPF to repair damaged lung tissue.

Mechanisms of interaction among the different cellular populations

Although not exactly known the initial lesion at the onset of the epithelial injury, it is generally considered that genetic predisposition (protein deficiency, telomere shortening) is associated with other external triggers such as lung toxins, infections, or repeated microaspirations could start the harmful process.

As a result of the damage caused on the alveolar epithelial and basal membrane, and activation of alveolar wall cells releasing growth factors and inflammatory cytokines including interleukins, MCP-1, and profibrotic molecules such as PDF and TGF-beta. Thus, the loss of alveolar cells and the presence of inflammatory molecules would generate a favorable microenvironment to perpetuate a pathological fibrotic process.

In turn, the soluble mediators produced by the epithelial and endothelial inflammatory cells would activate the circulating cells, including the fibroblasts, to maintain the injurious response.

The fibroblasts would respond to these molecules through their proliferation and differentiation into myofibroblasts grouped in fibrotic foci, which would precede the development of advanced phases of pulmonary fibrosis. On the other hand, the exhaustion and loss of the regenerative capacity of the mesenchymal progenitor cells exposed to the mentioned inflammatory microenvironment would play an essential role in the perpetuation of fibrosis.

The synthesis and progressive deposition of collagen in the extracellular matrix would alter the pulmonary structure and progressive and irreversible loss of its functional capacity.

ROLE OF AGING IN IPF CELLULAR MECHANISMS

Accelerated aging of the lung has been proposed as an essential mechanism in IPF. A series of aberrant hallmarks shared by chronic

degenerating conditions such as cancer, fibrosis, and aging have been described. They include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Table 2).

These mechanisms are involved in progressive loss of cellular physiological integrity, including different subpopulations of alveolar epithelial cells and interstitial fibroblast and mesenchymal progenitor cells. If their normal function is altered, they can derive into different phenotypes acquiring new roles. This would result in the aberrant activation of epithelial cells, which secrete numerous mediators, resulting in expansion of the fibroblast/myofibroblast population with the subsequent exaggerated accumulation of extracellular matrix and destruction of the lung architecture[58-61] (Fig. 1).

Table 2. Aging mechanisms linked to IPF

Aging mechanisms
1. Internal factors. – Defects in the mechanisms of DNA repairment causing gene variations which predispose to the development of IPF. – Telomeric shortening producing loss of protective sequences and the ends of the chromosomes which limits the proliferative capacity and induce cellular senescence. – Mitochondrial dysfunction in epithelial cells, fibroblast and macrophages inducing the production of reactive oxygen molecules, metabolic changes and secretion of cytokines that could lead to cellular apoptosis. – Loss of protein homeostasis and reduction of elimination of the damaged proteins leading to anomalies that affects the normal cellular autophagy. – Cellular senescence
2. External factors: smoking habit, environmental pollution, respiratory tract infections, gastroesophageal reflux.

*Genetic factors

Different genetic disorders associated with IPF have been reported. One of the most studied is the gene MUC5B which presents overexpression due to the polymorphism of a single nucleotide (rs35705950) that codes for mucin 5B. It is known that this glycoprotein intervenes in mucociliary clearance and the response of innate immunity[62]. Although the mechanism by which overexpression of the gene increases the possibility of developing IPF up to 30-50% is still unknown, its identification would help for the early detection of the subjects with a higher risk of developing the disease in the most incipient phase[63].

Genes associated with a higher risk of suffering from IPF and associated with a worse prognosis are TERT, TERC, RTEL1, and PARN[64]. These are involved in the maintenance of telomere length, an essential mechanism to regulate cellular aging, as will be discussed later.

Other variations of genes predisposing to the disease (DSP, AKAP13, CTNNA, and DPP9) are known, which are responsible for adhesion and cell integration[65-66]. Among the genetic factors, the instability caused by defects in DNA repair mechanisms may contribute to the risk of developing pulmonary fibrosis. In addition, changes through DNA methylation, histone modification, and non-coding RNA have been proposed as a hallmark of aging by which chromatin remodeling would alter gene expression[65]. The dysregulation of growth factors and the activation of the IGF-1/AKT/mammalian target of rapamycin (mTOR) axis that also actively participates in the pathogenesis of IPF should be taken into account[67].

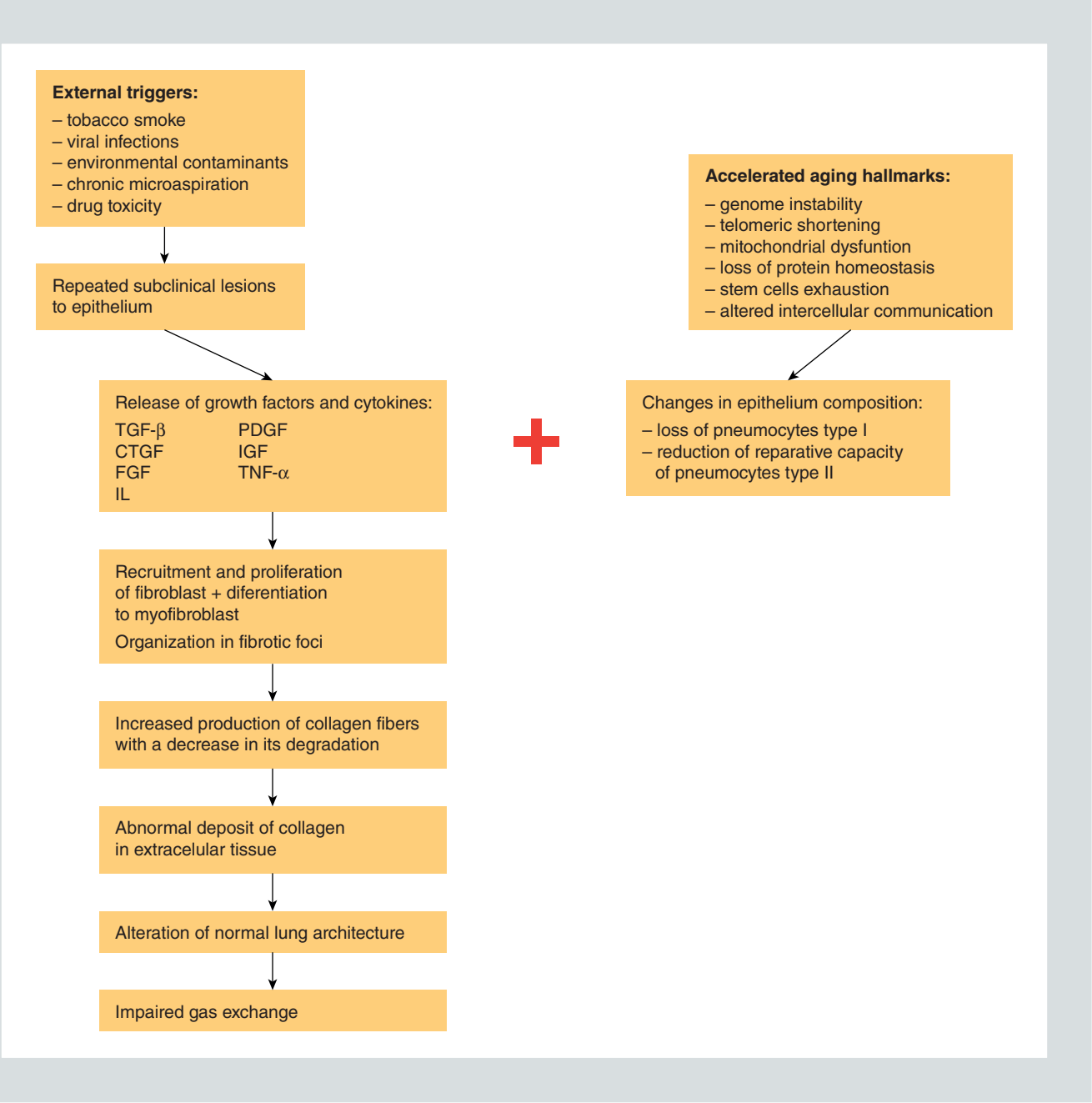

Figure 1. Schematic view of the pathophysiological mechanisms involved in the development of IPF.
CTGF: connective tissue growth factor; FGF: fibroblast growth factor; IGF: insulin-like growth factor; IL: interleukin; IPF: idiopathic pulmonary fibrosis; PDGF: platelet-derived growth factor; TGF-β: transforming growth factor beta; TNF-α; tumor necrosis factor-alpha.

Nevertheless, the genetic factors determine the expression of the disease and take into account the microenvironment to which the cells are exposed as well as different external factors that will constitute a risk factor for the development of the disease. Among these factors, we would highlight advanced age, male sex, or smoking habit as the best known. However, other factors have also been related, such as gastroesophageal reflux[68], sleep

apnoea/hypopnoea syndrome (SAHS)[69], environmental pollution[70], changes in the microbiome[71], infection by herpesvirus[72], and other occupational exposures interstitial lung disease (ILD) (to vapors, gas, dust, and fumes)[73].

Telomeric shortening

Telomeres are mainly involved in the control of cell growth. Although these are protective sequences at the ends of the chromosomes, they limit the proliferative capacity and induce cellular senescence, a determining factor in pulmonary fibrosis. Knowing if this alteration exists is essential since its severity correlates with the progression of the disease[74].

To avoid this process of DNA loss, there is a specialized DNA polymerase called telomerase, whose function consists in the repeated addiction of telomeres to the ends of the chromosomes[75]. Thus, the appearance of a mutation would cause enzymatic dysfunction and consequently telomeric shortening in the lung epithelial cells and several subclasses of leukocytes. Telomerase dysfunction together with mutations of surfactant proteins would be well described in cases of familiar IPF with a prevalence of 8-15% and 1-3% of cases of sporadic pulmonary fibrosis[76].

We should highlight in this last subgroup the influence of other epigenetic factors, as discussed above, that could contribute to this process of accelerated cellular aging leading to telomere alteration in the absence of telomerase mutations[77].

Recent studies have discovered a telomerase activator that can suppress the process of pulmonary fibrosis in animal models[78]. It is important, however, to underline the hypothesis that not all the telomere shortening process depends on this enzyme, but that other external factors intervene, also influencing the type of affected cell. In favor of this theory, there are studies carried out with mice with deficiency of the telomerase gene that do not develop signs of pulmonary fibrosis on their own, but that, in combination with exposure to toxic substances such as tobacco, can lead to pulmonary emphysema, a disease also related with cell aging[79].

Mitochondrial dysfunction

The mitochondria are essential for the production of energy through oxidative phosphorylation and the regulation of critical cellular processes, including cell death and inflammation. Thus, a currently significant line of investigation includes the study of molecular mechanisms that regulate mitochondrial processes such as metabolic changes, production of reactive oxygen species (ROS), the appearance of mitochondrial DNA mutations as well as mitochondrial signaling anomalies[80]. Recently, dysregulation of many of these mechanisms has been identified in epithelial cells, fibroblasts, and lung macrophages in patients with IPF[81].

Exposure to harmful agents could lead to cellular apoptosis through an increase in ROS production by epithelial cells[82]; said reactive oxygen molecules would produce cellular damage and, consequently, accelerated aging. Another route of ROS production would be through the alveolar macrophages that would also enhance the secretion of TGF-B1. This

molecule is responsible for providing resistance to mitochondrial autophagy, being this the mechanism by which the cell eliminates those dysfunctional mitochondria. Multiple membrane proteins mediate this process. The best known is PINK1, having shown in several studies that its deficiency prevents the correct mitophagy and consequently produces the accumulation of dysfunctional mitochondria contributing to cellular senescence[83].

However, the role of reactive oxygen species produced by mitochondria in cell aging is not yet clear, as other authors have described how, in animal models, the increase in ROS and oxidative damage do not accelerate cellular aging[84-89]. Instead, this could be explained by increased ROS production in response to stress and cell damage as a mechanism to maintain survival.

Another mechanism that induces the death of alveolar epithelial cells is the deficiency of deacetylase sirtuin-3 that would cause the inactivation of 8-oxoguanine DNA glycosylase. This would lead to a loss of its function to protect mitochondrial DNA from oxidative mechanisms[90].

Loss of proteostasis/autophagy

Proteostasis (homeostasis of proteins) is the process that comprises the different pathways involved in the biogenesis, folding, function, and degradation of cellular proteins. With cellular aging, there is an alteration of the proteostasis and, consequently, anomalies that induce the stress of the endoplasmic reticulum (ER). This activates the adaptive unfolding protein response (UPR) that stops the general synthesis of proteins and increases the synthesis of chaperones (HSP70, HSP90, DNAJ / HSP40, chaperonin/HSP60, and small HSP), a set of proteins responsible for facilitating the folding of proteins, the traffic, and activity of lysosomal enzymes[91]. It has been observed that high levels of ER stress markers and activation of UPR are found in pulmonary alveolar epithelial cells[92].

To eliminate excessive or misfolded proteins (proteolysis), the proteasomal system of ubiquitin and autophagy are used, which, in diseases associated with aging such as IPF, are reduced in parallel exacerbating stress enhancing the senescence of the cells involved in the pathogenesis of the disease[93].

In pulmonary fibrosis, levels of light chain 3-II (LC3-II), a marker of autophagy, are significantly lower than in the general population[94]. However, the main one in charge of diminishing autophagy and enhancing the resistance to apoptosis of fibroblasts in the IPF is mTOR through the persistent activation of the mTORC1 pathway. This would be responsible for maintaining low levels of cellular autophagy. This pathway could suppose a possible therapeutic target to induce the apoptosis of the fibroblasts using two inhibitors: rapamycin and PP242, as some in vitro studies have shown[95]. In addition, blocking the mTOR pathway by rapamycin has also been shown to attenuate pulmonary fibrosis induced by TGF-β in mice[96].

Studies are currently being conducted to prevent proteostasis loss by modifying proteolysis systems or altered chaperones such as BiP or HSP40 using compounds that modify intracytoplasmic calcium levels more significant

transcription and translation of these proteins[97]. One of the most promising research drugs that rescue the folding of mutant proteins and promote toxic aggregates' clearance is the regulatory chaperone of proteostasis, 4-phenyl butyric acid (4-PBA)[98]. It is known that 4-PBA improves bleomycin-induced pulmonary fibrosis and decreases the expression of stress markers ER, collagen and α-smooth muscle actin (αSMA)[99].

Cellular senescence

Cellular senescence is defined as a stable arrest of the cell cycle. It contributes to accelerating pulmonary aging, which in turn leads to an impaired lung function.

Several factors are related to the development of a dysfunctional cellular phenotype. For instance, toxins such as air pollution, lead, nitrosamines, or tobacco smoke generate ROS production and induce mitogenesis, therefore damaging DNA and causing telomere shortening[100]. Other substances like chloroquine and heavy metals lead to a disruption of cellular proteostasis[101].

These cellular alterations are associated with a shift in nutrient utilization to favor glycolysis instead of mitochondrial oxidative phospholiration[102]. Due to inefficient and slow ATP production, the cell progressively accumulates excess ADLP and AMP and halts its capacity to proliferate since this process requires rapidly available energy. AMC is the preferred substrate for AMPK leading to activation of p53/p21 and Prb/p16 pathways[103]. The pyruvate produced is transferred to the mitochondria causing cellular swelling, a morphological biomarker to identify senescent cells. Also, the enzymatic conversion of pyruvate in the mitochondria generates Acetyl-CoA, which is utilized in the nucleus as acetyl donors to remodel histone structure and regulate cell transcription[104].

All these combined lesions in the senescent cells are linked to the development of a senescent associated secretory phenotype (SASP) promoting the expression and release of highly inflammatory factors, including tumor suppressor proteins, transcription factors, microRNAs, growth factors, proteases, and inflammatory cytokines (ß-galactosidase, IL-6, IL-1b, NF-KB, p161NK4a)[105]. The secretory phenotype of these senescent cells is sufficient to trigger changes in the surrounding tissue and causing systemic effects.

In IPF, it is possible to detect these changes in all cell types involved in both animal and human models[106]. The senescence of myofibroblasts accompanied by the production of proinflammatory cytokines and metalloproteinases in the extracellular matrix contributes to the lung parenchyma's progressive fibrosis[107].

Advancing in the knowledge of the pathways of the senescence process would allow us to develop possible therapeutic targets. For instance, senescent fibroblasts exhibit an increased ROS-generating enzyme Nox4 and low levels of the critical mediator of the cellular antioxidant response pathways NFE2, generating an imbalance that contributes to the senescence process. It has been shown that treatment with a Nox inhibitor restores the redox balance and results in a decrease in senescent cells and a reduction in lung fibrosis[108].

CONCLUSIONS

Current theories on the pathogenesis of IPF include an initial lesion on the alveolar epithelial cells and the basal membrane that will trigger the production of inflammatory and profibrotic mediators, which in turn will induce changes in fibroblast proliferation, increased deposits of proteins in the extracellular matrix as well as cellular apoptosis and abnormal repair of tissue damage.

This pathology's progressive and irreversible nature means that it has a poor prognosis in the short term. Currently, few therapeutic options have been shown to modify the evolution of the disease.

Hence the need to understand the physiopathological mechanisms involved in the development of the disease. Only by understanding its pathogenic mechanisms it will be possible to recognize routes with the potential to become new therapeutic targets that can be used to improve the quality of life and the survival of these patients. Thus, the cellular mechanisms of aging continue to be a potential therapeutic target in which we must continue researching and investing resources to change the future of this disease.

DISCLOSURES

Dr. Cuerpo, Dr. Albacar, and Dr. Rojas have nothing to disclose.

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