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Aging and Pulmonary Fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis is a chronic, progressive, and usually fatal lung disorder of unknown etiology. The disease likely results from the interaction of genetic susceptibility architecture, environmental factors such as smoking, and an abnormal epigenetic reprogramming that leads to a complex pathogenesis. Idiopathic pulmonary fibrosis occurs in middle-aged and mainly elderly adults, and in this context age has emerged as its strongest risk factor. However, the mechanisms linking it to aging are uncertain. Recently, nine molecular and cellular hallmarks of aging have been proposed: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. In this review, we provide an overview of these molecular mechanisms and their involvement in the pathogenesis of idiopathic pulmonary fibrosis, while emphasizing that the studies on this disease are few and the findings are not definitive. (REV INVES CLIN. 2016;68:75-83)

Key words: Aging. Lung fibrosis. Senescence. Telomeres.

INTRODUCTION

Biological lung aging is characterized by structural changes and progressive loss of physiological integrity, leading to impaired function[1]. Although the mechanisms that contribute to the aging process are uncertain, nine putative hallmarks associated with the aging phenotype have recently been proposed[2]. However, in what way and magnitude they participate in the aging lung is unknown.

FUNCTIONAL AND STRUCTURAL MODIFICATIONS OF THE LUNGS AND THORAX DURING AGING

In general, "normal aging" is characterized by narrowing of the intervertebral disk spaces and increased prevalence of hyperkyphosis. In fact, 20-40% of older adults present an excessive curvature of the thoracic spine[3]. In addition, there are changes in the intrinsic function of the muscles, which are associated with reduced inspiratory

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Figure 1. Expiratory high-resolution computed tomography scan revealing inhomogeneous lung attenuation due to air trapping identified by the presence of areas of low attenuation next to regions with normal attenuation (arrows).

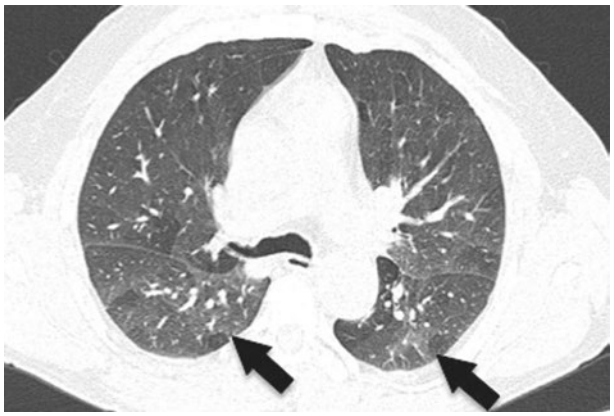
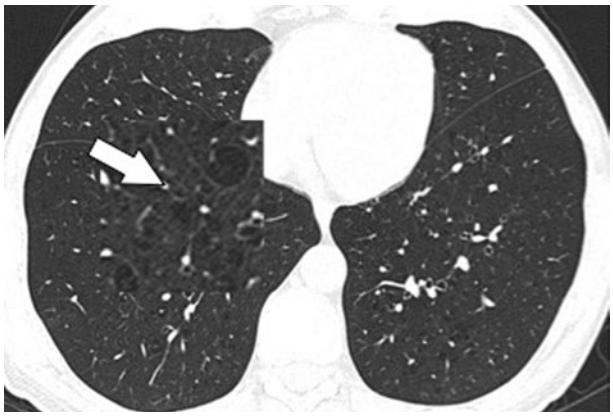


Figure 2. Early stage of centriacinar emphysema in a 73-year-old asymptomatic individual. High-resolution computed tomography demonstrates numerous tiny low attenuation areas throughout the lung field (arrow).



and expiratory respiratory muscle strength. This process, together with a decrease in the mitochondrial adenosine triphosphate (ATP) reserves, contribute in older individuals to having difficulties in sustaining a sudden rise in metabolic demand, increasing the risk of respiratory failure in acute lung diseases.

A common finding with aging is a decrease of lung elasticity[4]. This affects the small airways and alveolar septa, and may explain at least two frequent observations in the elderly. The first is a premature collapse of the peripheral airways, which provokes the so-called "air-trapping" that is more evident during expiration (Fig. 1). The other is the increase in size of the alveolar ducts and alveoli, which was previously called "senile emphysema", although this is not an appropriate term since it lacks the characteristic destruction of the alveolar walls seen in emphysema (Fig. 2). Nevertheless, the alveolar over-distention results in an increase of the residual volume of about 5-10% per decade[5].

Other studies performed in older individuals (> 75 years old) without known respiratory disease have also reported the presence of reticular opacities (suggestive of fibrosis), as well as airway dilation, bronchial thickening, and bronchiectasis when compared with younger (< 55 years old) subjects[6]. Changes in the airways are associated with dysfunction of the mucociliary escalator, decreased capacity to clear mucus and particles from the lungs, and a reduction in cough strength[7]. We have found similar alterations in an ongoing study on aging lung in asymptomatic individuals (Selman, et al., unpublished results) (Fig. 3).

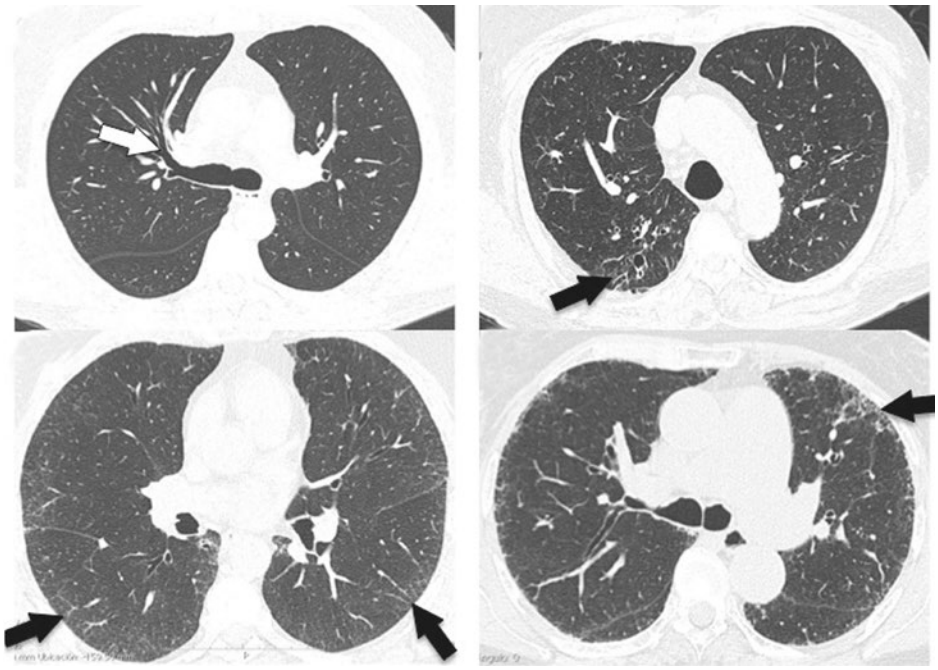
Physiological age-related pulmonary changes are characterized by a decrease of approximately 30 ml each year in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)[8,9]. Likewise, the mentioned increase in the closing volume by the premature collapse of the small airways, combined with diverse age-related changes in the pulmonary circulation, result in a heterogeneous distribution of the ventilation/perfusion ratio. This, together with a decrease in the diffusing lung capacity for carbon monoxide (DLCO), causes an age-related decline in the arterial tension for oxygen (PaO_2)[10-12].

LUNG DISEASES ASSOCIATED WITH AGING

There are two types of lung disorders associated with aging: those that may occur at any period of life but whose severity is affected by aging, and those that occur virtually only in old people. Among the first type, asthma, obstructive sleep apnea, and pulmonary edema in the setting of congestive heart failure are some of the most common[13,14]. Likewise, decreased respiratory muscle strength, attenuated cough, dysfunction of mucociliary clearance, and altered immune response increase the risk for lung infections in elderly patients[13].

By contrast, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are two diseases usually diagnosed in individuals over 50 years old and whose incidence and prevalence increase remarkably with age. Thus, the prevalence of COPD in persons aged 65 years and older in the

Figure 3. High-resolution computed tomography showing several abnormalities detected in elderly asymptomatic subjects. **A:** Central airway dilation. **B:** Bronchiectasis. **C:** and **D:** Peripheral, subpleural septal thickening (arrows).



general population is at least 10-15%[15]. The real incidence and prevalence of IPF are uncertain, but in the USA it has been reported that the incidence is about 10 per 100,000 persons per year, which increases to approximately 90 per 100,000 per year in people aged 65 years and older[16,17].

IDIOPATHIC PULMONARY FIBROSIS: THE INFLUENCE OF AGING

Idiopathic pulmonary fibrosis is a progressive, irreversible, and usual fatal lung disorder of unknown etiology[18]. It has been proposed that the disease is triggered by an aberrant activation of alveolar epithelial cells (AEC), which in turn induces the migration, proliferation, and activation of fibroblasts/myofibroblasts, leading to the exaggerated accumulation of extracellular matrix and the subsequent destruction of the lung architecture[19]. As mentioned before, IPF occurs in middle-aged and mainly elderly adults, suggesting a mechanistic link between chronological age and this disease. However, the biopathological mechanisms that link aging with the pathogenesis of IPF have not been elucidated.

Recently, nine putative cellular and molecular hallmarks were proposed to contribute to the aging processes and aging phenotype[2]. Although studies in IPF are few, almost all of these hallmarks have been examined and results suggest that an accelerated aging process occurs in this disease.

GENOMIC INSTABILITY

Age-dependent accumulation of DNA damage is a well-recognized component of the aging phenotype[2]. Several studies have reported the presence of genomic instability in IPF patients[20-22]. The incidence of microsatellite instability (MSI) and loss of heterozygocity (LOH) were determined in cytological sputum specimens from 26 IPF patients and 26 matched controls using 10 highly polymorphic microsatellite markers[20]. Fifty percent of the patients displayed genetic alterations, either MSI or LOH. The most commonly affected microsatellite markers were THRA1 and D8S133. Subsequently, a one-base-pair deletion was detected in the polyadenine tract in exon 3 of the transforming growth factor (TGF)-beta RII receptor gene in AECs isolated by microdissection from IPF lungs. Furthermore, in these areas, low expression of the receptor was confirmed[21]. Finally, 40 microsatellite markers were evaluated in 52 sputum/venous blood DNA pairs from IPF patients[22]. Twenty specimens (38.5%) exhibited LOH in at least one of the examined loci; LOH

was observed in microsatellite DNA markers located in MYCL1, FHIT, SPARC, p16Ink4, and TP53 genes. Taken together, these findings indicate that genetic instability likely affecting genes involved in critical cellular pathways is a relatively frequent phenomenon that could account for the pathogenesis of IPF.

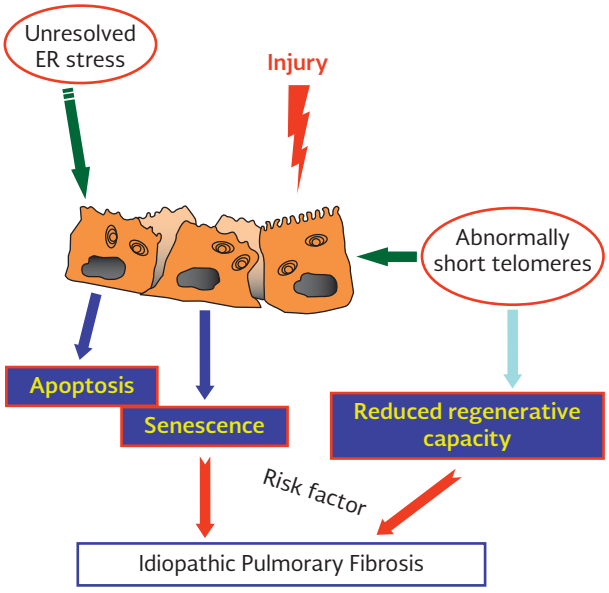
TELOMERE ATTRITION

Telomere shortening is considered one of the most influential mechanisms of cellular aging. When telomeres become critically short, they activate a DNA damage response that provokes cellular senescence or apoptosis[23]. Abnormal telomere shortening has been associated with several progressive disease phenotypes that share the short telomere defect as a driving mechanism[23]. Telomerase mutations cause approximately 20% of the cases of familial IPF (identified by the presence of two or more individuals in a family having pulmonary fibrosis), and all of these patients characteristically have very short telomeres[24-26]. Furthermore, 20-30% of patients with sporadic IPF that do not have mutations in telomerase components displayed telomere lengths less than the 10th percentile when compared with control subjects[27]. The mechanisms by which telomere defects contribute to IPF are uncertain. It has been proposed that telomerase mutations (familial IPF) or exaggerated proliferative response (sporadic IPF) lead to telomere shortening in the alveolar epithelium and that this is critical for the development of the disease. A recent study supports this notion[28]. In this work, late-generation telomerase-null mice induced by deleting telomeric repeat-binding factor 2 (Trf2) was generated, and in this conditional mutant model, where telomere dysfunction was restricted to type 2 AECs (AEC2), the stem cell function of this subpopulation was impaired, leading to senescence. Moreover, when telomere dysfunction was induced in purified adult AEC2s, *ex vivo* cells survived but remained senescent[28]. These results indicate that AEC2-dependent telomere dysfunction and senescence limit alveolar repair and can signal mesenchymal abnormalities (Fig. 4).

CELLULAR SENESCENCE

Cellular senescence has been considered a critical event in biological aging. It refers to a permanently arrested state of cell growth together with the achievement of

Figure 4. Alveolar epithelial cells play a critical role in the pathogenesis of idiopathic pulmonary fibrosis. Unsolved endoplasmic reticulum stress and extreme shortening of telomeres may lead to epithelial cell death or senescence, and the senescence-associated secretory phenotype characterized by the upregulation of genes encoding a complex pro-inflammatory and profibrotic transcriptional response. ER: endoplasmic reticulum.



the senescence-associated secretory phenotype, characterized by the release of a variety of inflammatory, growth-regulating, and tissue-remodeling factors[2,29].

Recently, AEC senescence was revealed in IPF lungs[30]. In this study, strong staining of β-galactosidase, a marker of senescence, and p21/waf-1, a senescence-associated cyclin-dependent kinase inhibitor, was observed in the lung epithelium. These results were confirmed in a second study where nuclear staining of p21 was clearly demonstrated only in epithelial cells covering actively fibrosing lesions, while β-Gal-positive staining was observed in epithelial cells covering fibroblastic foci[31]. Alveolar epithelial senescence, likely related to shortening of telomeres, may contribute to the high secretory profile exhibited by these cells in IPF.

On the other hand, studies on fibroblasts have given elusive results. Recently, a study demonstrated that fibroblasts within fibroblastic foci of IPF lungs show features of senescence. Expression of p16 and p21 was seen in fibroblasts within the foci and in the overlying epithelial cells[32]. Moreover, fibroblast expression of NADPH oxidase-4 (Nox4) was increased in IPF lung

fibroblasts, and the use of a specific inhibitor attenuated βgal activity, suggesting that Nox4 contributes to cellular senescence of IPF fibroblasts. More recently, a study showed that IPF fibroblasts displayed an accelerated entry to replicative senescence, accompanied by an accumulation of senescent cells with features of myofibroblasts characterized by high expression of alpha smooth muscle actin (α-SMA)[33].

There is also some "systems senescence" in IPF patients, e.g., immune senescence or endocrine senescence, which may contribute to the development or progression of IPF. For example, a marked downregulation of CD28 on circulating CD4 T-cells has been found in IPF patients compared with age-matched controls[34]. CD28 is a major co-stimulatory molecule responsible for the optimal activation of naive T-cells. It is also involved in proliferation, survival, and glucose metabolism. The T-cells lose CD28 expression with age, often taken as a hallmark of aging human T-cells[35].

Deterioration of the endocrine system also occurs during aging and is thought to contribute to increased susceptibility to aging-associated diseases. In this context, we evaluated the blood levels of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEA-S), the most abundant adrenal steroids in humans. Under physiological conditions, DHEA/DHEA-S reach a peak between the ages of 25 and 30 years and thereafter gradually decline so that, by the age of 60, the concentrations are only 10-20% of corresponding values in young adults[36]. We found that IPF patients had a disproportionate decrease in the circulating levels of DHEA-S compared with age-matched controls. Moreover, DHEA displayed a strong antifibrotic effect on fibroblasts, affecting migration, proliferation, differentiation to myofibroblasts, collagen synthesis, and survival, indicating that its exaggerated decline may participate in the pathogenesis of the disease[36].

MITOCHONDRIAL DYSFUNCTION

Mitochondria play a key role in cellular homeostasis, bioenergetic capacity, and longevity since they are the highest producers of ATP and regulate programmed cell death. Aging is associated with the expansion of dysfunctional mitochondria, with alterations in mitochondrial dynamics and quality control processes resulting from an imbalance of fission and fusion events and increased production of reactive oxygen species (ROS)[37]. Mitochondrial DNA (mtDNA) is damaged by ROS generated during oxidative metabolism, and the accumulation of damaged mtDNA and decreased mitophagy result in loss of fidelity in the synthesis of new mitochondria proteins, leading to senescence and aging[2].

Excessive production of ROS and disruption of the oxidant/antioxidant balance in the lung have been found in IPF[38]. In the expired breath condensate, the concentrations of H_2O_2 and 8-isoprostane, which are markers of oxidative stress, are usually increased in IPF patients compared with normal controls, indicating high levels of oxidative stress[39]. Likewise, a marked reduction of levels of glutathione, a major antioxidant molecule, has been observed in bronchoalveolar lavage, sputum, and plasma of patients with IPF[40,41].

Recently, a study demonstrated that AEC2 of IPF lungs exhibit an age-related mitochondrial dysfunction with altered structure and impaired mitophagy[42]. Deficiency of PTEN-induced putative kinase 1 (PINK1) was identified as a fundamental mechanism leading to accumulation of dysfunctional mitochondria and, moreover, the mitochondrial phenotype observed in IPF lungs and susceptibility to lung fibrosis was recapitulated in an animal model of aging and PINK1 deficiency. Importantly, several chronic degenerative diseases associated with aging, such as Parkinson's disease and neuropsychiatric disorders, present mutations or deficit of PINK1 and show swollen and dysfunctional mitochondria and poor mitophagy, indicating that this may be a common phenomenon in aging-associated diseases.

LOSS OF PROTEOSTASIS

Aging and some aging-related diseases are associated with impaired proteostasis. Protein homeostasis involves mechanisms for the stabilization of correctly folded proteins and mechanisms for the degradation of proteins by two principal proteolytic systems implicated in protein quality control: the autophagy-lysosomal system and the ubiquitin-proteasome system[2]. There is a strong body of evidence indicating that aging is associated with disturbed proteostasis, which may contribute to age-associated disorders. Furthermore, maintenance of appropriate autophagic activity prevents or slows down the functional failure

associated with cellular proteotoxicity and accumulation of intracellular damage in aging[43].

Recent work has approached the putative role of autophagy in IPF, while studies on the ubiquitin system are scant.

Autophagy is a complex process involving multiple proteins and steps, including the formation of an initiation complex and development of a double-membrane phagophore; elongation of the membrane and completion of an autophagosome vesicle around cargo; lysosomal fusion; dissolution of the inner membrane allowing hydrolases to degrade the cargo; and recycling of the components[44].

In the first approach in IPF, it was reported that LC3-II levels (commonly used as a marker of autophagy) were significantly lower in whole tissue homogenate of lungs from patients with IPF compared with control lungs. In experimentally induced lung fibrosis, it was shown that the inhibition of mTORC1, a primary modulator of autophagy, with rapamycin attenuated the fibrotic response[45]. In this study, they also found that inhibition of autophagy potentiated fibroblast to myofibroblast differentiation and activation. A subsequent study, using biochemical evaluation of *in vitro* models, demonstrated that autophagy inhibition is sufficient to induce acceleration of epithelial cell senescence and myofibroblast differentiation in lung fibroblasts[31]. More recently it was shown that an aberrant PTEN/Akt/mTOR axis desensitizes IPF fibroblasts from polymerized collagen-driven stress by suppressing autophagic activity, which produces an IPF fibroblast phenotype resistant to apoptosis in collagen[46].

Most studies regarding the role of autophagy in lung fibrosis have focused on fibroblasts. A more recent work suggests that epithelial cells may also be affected. In an experimental model induced by bleomycin, it was shown that Atg4b-deficient mice exhibited reduced autophagy and a significantly higher inflammatory and fibrotic response compared with the wild-type littermate. Importantly, the study found that Atg4b disruption resulted in increased apoptosis, affecting predominantly alveolar and bronchiolar epithelial cells[47]. These findings indicate that autophagy protects epithelial cells against bleomycin-induced stress and apoptosis, and participates in the attenuation of the inflammatory and fibrotic responses.

Importantly, evidence suggests that there is an age-related decline in autophagy and selective targeting of mitochondria for autophagic degradation that enhances the lung fibrotic response in experimental models[48]. This reduction seems to be exaggerated or accelerated in IPF, a natural aging-associated human fibrosis.

Oxidative stress, endoplasmic reticulum (ER) stress, and hypoxia, all mechanisms that participate in the pathogenesis of IPF, are well-known inducers of autophagy. However, this protective mechanism is dysfunctional, likely contributing to the pathobiology of the disease.

The ubiquitin-proteasome system is the major degradation pathway for short-lived proteins in eukaryotic cells. Its relevance for preservation of protein homeostasis in the lung is emerging for chronic lung diseases[49]. In this context, inhibition of this system by specific proteasome inhibitors has been shown to provide antifibrotic effects in the mouse model of bleomycin-induced lung damage[50].

However, the regulation of proteasome function in IPF has not been explored in detail. Recently, a study showed that the proteasome is activated in the process of TGF-β-induced human myofibroblast differentiation[51]. The activation resulted from increased formation of 26S proteasomes. In IPF lungs, the expression of the subunit Rpn6 was upregulated specifically in myofibroblasts and hyperplastic AECs overlying fibroblast foci. Elevated levels of K48-polyubiquitin protein conjugates in these cells and the positive correlation of whole lung Rpn6 protein levels with K48-polyubiquitinated proteins suggest that activation of ubiquitin-dependent protein degradation by the 26S proteasome may be a pathologic feature of fibrotic remodeling occurring specifically in IPF[51].

STEM CELL EXHAUSTION

The balance between stem cell self-renewal and differentiation is critical to orchestrate tissue homeostasis and the response for repair/replacement of damaged tissues. In this context, a major hallmark of aging is a reduced ability to regenerate, which has been associated with a decline in proliferative activity, impaired function, and exhaustion of tissue-specific stem and progenitor cells[2]. There is an emerging

body of evidence indicating that reduced function of adult stem cells plays an important role in the development of age-related diseases[52]. So far, no studies in IPF have been published. In a recent report, bone marrow-derived mesenchymal stem cells (B-MSC) derived from old animals were found to display a remarkable downregulation of multiple chemokine receptors such as CCR7, CX3CR1, and CXCR5 as well as other genes involved in migration[53]. When lungs were injured with *Escherichia coli* lipopolysaccharide, aged endogenous B-MSCs not only failed to migrate appropriately to the injury site, but once there they also failed to produce enough of the anti-inflammatory agents that characterize their younger forms. Interestingly, there were similar differences between B-MSCs obtained from young and aged human individuals; that is, old cells showed a downregulation of cytokine receptors, decrease in activation, and migration.

DEREGULATED NUTRIENT-SENSING

Insulin-like growth factor (IGF-1) and insulin signaling are known as the "insulin and IGF-1 signaling" and represent the most conserved aging-controlling pathway in evolution[2]. Among its multiple targets are the mammalian target of rapamycin (mTOR) complexes, which are also involved in aging and recently have been implicated in lung fibrosis. For example, in a recent work, aberrant mTOR signaling activation was provoked in AECs using conditional *Tsc1* knock-down mice that were then injured with bleomycin[54]. Mice with increased mTOR activation exhibited high mortality and exaggerated lung fibrosis compared with control mice. Moreover, mTOR inhibition with rapamycin rescued bleomycin-mediated lung injury and fibrosis. These findings were associated to decreased autophagy that, as mentioned, seems to contribute to abnormal repair and fibrosis.

Supporting the role of mTOR complexes in the fibrotic response, a recent study in IPF lung fibroblasts demonstrated that TGF-β, a major profibrotic mediator, induced the Rictor component of mTORC2, which led to Akt activation[55]. Moreover, the use of a specific inhibitor of the active site mTOR attenuated the expression of profibrotic matrix-regulatory proteins in TGF-β-stimulated IPF fibroblasts and inhibited the fibrotic response in a murine bleomycin lung model[55]. Overactivation of mTOR has been found in fibroblast foci and alveolar epithelial cells of IPF lungs[54,56].

EPIGENETIC ALTERATIONS

Epigenetic mechanisms are heritable changes in gene activity that are independent of alterations in the underlying DNA sequence. In a more extensive definition, epigenetic includes the set of covalent modifications to DNA, posttranslational modifications to histones, and the regulatory effect of non-coding RNAs that influence the expression of genes and the structure of chromatin. All these epigenetic processes do not act independently, but strongly interact to form a complex regulatory system that can dynamically adjust the gene expression. Epigenetic marks are remodeled and may actively modulate the processes of aging.

DNA METHYLATION AND IDIOPATHIC PULMONARY FIBROSIS

DNA methylation is a covalent modification that occurs on cytosine, mostly located in CG dinucleotides (CpG). Cytosine methylation primarily happens in CpG-rich sequences, dubbed as CpG islands, resulting in the constitutive silencing of chromatin regions.

Aging is characterized by hypomethylation of sites outside promoter CpG islands, while CpG islands near promoters are typically hypermethylated, and there is some evidence indicating that these modifications in DNA methylation may be a sensor for both chronological and biological age[57].

Studies in IPF are scant and initially focused on putative meaningful candidate genes. Thus for example, Thy-1 (CD90), an important regulator of fibroblast behavior, is absent in myofibroblasts within fibroblastic foci in IPF, and its downregulation is mediated at least partially by the hypermethylation of the promoter[58]. Likewise, different levels of methylation of three CpG islands in the promoter of α-SMA in fibroblasts and myofibroblasts correlate with the levels of expression of this gene[59]. On the other hand, we have demonstrated that IPF fibroblasts have reduced expression of the proapoptotic p14ARF attributable to promoter hypermethylation, suggesting that epigenetic mechanisms may underlie their resistance to apoptosis[60].

Global methylation and gene expression patterns have been recently examined in IPF lungs[61]. By comprehensive high-throughput arrays, 4.6 million CpG sites

distributed across the human genome as well as the gene expression changes were examined in 94 IPF lungs and 67 controls. Over 2,000 differentially methylated regions associated with 1,514 unique genes were identified, with the majority of the methylation changes located outside of promoter CpG islands. Functional analyses identified several enriched canonical pathways that have been implicated in the pathogenesis of IPF, including CXCR4 signaling, thrombin signaling, Wnt/β-catenin signaling, and epithelial adherens junction signaling. Analysis of binding motifs in promoters revealed overrepresentation of regulators of lung development, specifically, β-catenin, GLI1, and FOXC2; this is important since the upregulation of developmental pathways is involved in the aberrant activation of epithelial cells[62]. These findings support the notion that several biologically relevant methylation-expression changes may contribute to the development of IPF.

NON-CODING RNA AND IDIOPATHIC PULMONARY FIBROSIS

Two main sub-groups of regulatory-type non-coding RNA (ncRNA) have been described: the short ncRNAs (< 30 nucleotides long), that include microRNAs (miRNA), short interfering RNAs (siRNA), and piwi-interacting RNAs (piRNA); and the long ncRNAs that contain over 200 nucleotides and seem to control genome activity at the chromatin level.

Epigenetic deregulation of ncRNAs, primarily miRNAs, has been observed in IPF. In fact, different studies have shown that approximately 10% of miRNAs are deregulated and an imbalance between profibrotic and antifibrotic miRNAs are thought to be linked to the development or progression of IPF[63,64]. The downregulated miRNAs include miR-326, let 7d, miR-26a, miR-29, miR-200, and miR-17~92, while miR-21, miR-154, 199a-5p, and miR-145 are upregulated. In general, all these miRNAs play roles in the TGF-β1 signaling pathway, fibroproliferation, lung epithelial cell development, and epithelial to mesenchymal transition, and their deregulation results in the facilitation of many profibrotic processes.

It is important to emphasize that all these epigenetic mechanisms are integrated through complex crosstalk pathways and feedback loops. For example, an association between aberrant DNA methylation and miRNA expression has been recently identified in IPF[65]. Thus, increased DNA methylation in the promoter of the miR-17~92 clusters silence its expression, which in turn results in the upregulation of genes strongly related to the fibroproliferative response and the fibroblast phenotype in IPF.

Finally, whether some of the mentioned epigenetic changes observed in IPF are related to aging is uncertain. It has been proposed that there is a stochastic age-related DNA methylation drift, which is bidirectional (both hyper- and hypomethylation), is not uniform across the genome, and is quite variable between individuals of the same age[66]. It is tempting to think that in few of them, the drift particularly affects genes whose up- or down-regulation results in a profibrotic reprogramming.

CONCLUSIONS

Aging is a multifaceted process that results in progressive decline in homeostasis and increased risk of disease or death. Incidence and prevalence of IPF increase remarkably with aging. Before 50 years of age, IPF is rare, but over 60 years old, the prevalence may be as high as 300/100,000, indicating a strong link between aging and IPF. Most of the hallmarks of aging seem to be involved in the development or progression of IPF. However, studies to date were performed in small cohorts and have produced heterogeneous results. In the future it will be necessary to integrate the genetic and epigenetic data to identify regulatory pathways associated with aging and identify which of them may be implicated in the pathogenesis of IPF.

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