

“I Just Don’t Have the Energy:” Aging Mitochondria and Pulmonary Fibrosis



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Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease characterized by progressive scarring of the lung [1, 2]. IPF prevalence dramatically increases with age, and aging is a known risk factor for IPF [3]. While *familial* pulmonary fibrosis has been associated with mutations in telomerase-related and surfactant proteins, the cause of the majority of *sporadic* IPF cases and the mechanisms involved in the aging susceptibility to IPF are unknown [4, 5]. One of the most compelling theories in IPF is the vulnerability of type II alveolar epithelial cells (AECII) to injury. This injury is associated with the presence of markers of cellular stress responses, secretion of pro-fibrotic cytokines, and increased apoptosis [6]. AECII are critical to regeneration of the injured lung. To repair the lung, AECII have high-energy demands and to accomplish this task, mitochondria accumulate in AECII, comprising approximately 50 percent of the lung mitochondrial mass [7, 8]. These observations suggested that mitochondrial dysfunction may be related to the pathogenesis of pulmonary fibrosis. We have found that the mitochondria in the AECII of IPF patients have an impaired capacity to repair the lung. The focus of our laboratory is to understand mitochondrial biology at the molecular level as a potential link between aging and the development of pulmonary fibrosis. We hope to uncover novel therapeutic targets to reverse mitochondrial pathology and ultimately IPF.

Mitochondria are the primary energy-generating organelles in most eukaryotic cells. While AECII are active progenitor and secretory cells with high-energy demands and high mitochondrial content, there is limited knowledge of the impact of aging on mitochondrial function

or the role of mitochondria on the susceptibility to lung disease. Aging seems to affect mitochondria in particular. Abnormalities in mitochondria are often observed with aging, including enlargement and loss of the membrane structures known as cristae [9, 10]. Moreover, ATP production and respiration in mitochondria from aged animals are less efficient compared to mitochondria from younger animals, and often, aging mitochondria produce increased amounts of potential injurious reactive oxygen species (ROS) [11].

In our laboratory, we have found that age affects mitochondria in AECII and leads to impaired respiration [12]. In addition, we discovered that AECII from patients with IPF are characterized by the accumulation of dysmorphic and dysfunctional mitochondria. These mitochondrial changes are also associated with increased expression of markers of endoplasmic reticulum (ER) stress-inducing (Figure 1). These findings were recapitulated in aging mice in response to ER stress-inducing stimuli. We found that dysfunctional mitochondria in AECII from IPF and aging lungs were related to low expression of the regulator of mitochondrial homeostasis, Phosphatase and Tensin Homolog induced putative kinase 1 (PINK1), a kinase linked to age-related neurodegenerative disease. We recently discovered that young PINK1-deficient mice exhibited elevated susceptibility to apoptosis and spontaneous TGF- β -driven lung fibrosis, developing similar dysmorphic and dysfunctional mitochondria in AECII [12].

PINK1 plays a crucial role in the maintenance of mitochondrial morphology, function, and selective degradation of damaged

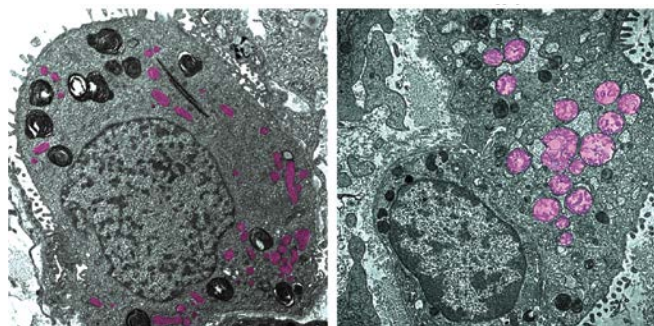


Figure 1. The morphology of mitochondria (fuscia) in alveolar type II epithelial cells changes from small oval dense morphology in a healthy lung to swollen in a lung with idiopathic pulmonary fibrosis (IPF).



mitochondria by cellular clean-up mechanisms known as mitophagy [13-15]. PINK1 has been extensively studied in the neuronal system as inherited mutations of PINK1 are associated with an early onset of Parkinson's Disease (PD) [16]. Models of PINK1 deficiency in *Drosophila*, zebrafish, and *in vitro* silencing of PINK1 result in impaired electron transport chain function, altered mitochondrial fission-fusion dynamics, increased oxidative stress, and changes in mitophagy, leading to cellular apoptosis. Interestingly, mice deficient in PINK1 show dysfunctional mitochondria in the heart and cerebral cortex with age or after exposure to cell stress, suggesting PINK1 has an important function as a regulator of mitochondrial stress responses [17, 18]. Thus, although PINK1 is ubiquitously expressed [19], PINK1 mutations can affect mitochondrial quality control differently according to cell type, age, and levels of cell stress [17]. PINK1 is highly expressed in epithelial and neural tissues but lower in tissues of mesenchymal origin with the exception of muscle [20]. In the lung, up-regulation of PINK1 has been found in lung epithelia of chronic obstructive pulmonary disease patients [21]. We have found that AECII, but not fibroblasts, from IPF lung are deficient in PINK1 expression, and this loss of PINK1 is associated with accumulation of dysmorphic and dysfunctional mitochondria and these cells elaborate many profibrotic factors [22].

Our discovery between mitochondrial dysfunction and induction of fibrosis suggests that therapeutic opportunities to improve mitochondrial function might have a beneficial effect in the prevention or therapy of lung fibrosis. Mitochondrial antioxidants have been developed, including Mito Q, and have shown improvement of respiratory function in mitochondria [26-28]. Metabolic substrates of the TCA cycle are under study as therapeutic candidates against cancer and pulmonary hypertension [29-31].

In summary, our studies indicated that aging and ER stress have important effects on the physiology of AECII mitochondria and influence susceptibility to lung fibrosis. We showed that aging and ER stress were associated with deficient expression of PINK1 in alveolar type II epithelial cells. As has been observed in neurons, PINK1 can regulate mitochondrial homeostasis in the alveolar epithelial cells, and its reduction can lead to the accumulation of enlarged and damaged mitochondria, loss of cell viability, and activation of profibrotic responses. These data suggest that therapeutic pathways based on induction of PINK1 and/or improvement of mitochondrial function, dynamics, and turnover might be useful in the treatment of lung fibrotic diseases.

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Case Presentation: Lymphocytic Interstitial Pneumonia



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John is a 64-year-old retired chemist with a history of IgG4-related pancreatitis who presented to the Simmons Center with a subacute onset of dyspnea on exertion, cough, and an abnormal chest CT scan. He was diagnosed with IgG4 disease in 2011, when he experienced weight loss, parotid enlargement, and pancreatitis. He was treated with prednisone, experienced no more episodes of pancreatitis, and was transitioned to mycophenolate for maintenance immunosuppression. At that time, a serologic workup was negative including ANA, ANCA, anti-SSA, and anti-SSB among others. He also never had elevated peripheral levels of IgG4.

He was referred to the Simmons Center in 2015 for evaluation of IgG4-related lung disease. His pulmonary symptoms were relatively mild with only mild dyspnea on exertion and a chronic



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cough occasionally productive of clear sputum. We completed pulmonary function testing that revealed a mild obstructive ventilatory defect. His CT chest scan (Figure 1) showed clusters of nodules in an interstitial pattern that had progressed compared with prior studies in 2012 and 2014. We discussed his case at the Simmons Center multidisciplinary case conference, which consists of pulmonologists and experts in rheumatology, radiology, and pathology. We concluded that several features of his case were not consistent with IgG4-related pulmonary disease, including the absence of peripherally elevated IgG4 levels and atypical imaging characteristics. In consultation with our rheumatology colleagues, we were concerned for seronegative Sjögren's disease, which can also present with parotid swelling and pancreatitis. We were also concerned about atypical infection in

(Continued on Page 4)