Mitochondrial Dysfunction as a Pathogenic Mediator of Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis

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Abstract

The mechanisms underlying the pathogenesis of chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis, remain incompletely understood. Mitochondria are vital cellular organelles crucial for energy generation, the maintenance of cellular metabolism, calcium homeostasis, intracellular signaling, and the regulation of cell death programs. Emerging evidence suggests that mitochondrial dysfunction plays a cardinal role in the initiation and progression of many human diseases, including chronic lung diseases. Upregulation of the autophagy program, a cellular adaptive mechanism for protein and organelle turnover, can occur in response to injury and may have a cell type-specific impact on the progression of disease. The selective autophagy subtype specific for mitochondria (mitophagy), regulated by PINK1 (phosphatase and tensin homolog-induced putative kinase 1), is a cellular response to accumulation of depolarized or injured mitochondria. Autophagy and mitophagy may be associated with

either cellular protection or propagation of injury in a cell type-specific manner, and they may also be associated with modulation of cell death pathways. Genetic studies in mouse models have revealed opposing roles for PINK1 and/or mitophagy in the propagation of emphysema and fibrosis, whereas human studies have shown altered regulation of PINK1 in both idiopathic pulmonary fibrosis and COPD. We have also recently identified a role for mitophagy in regulating the cellular necroptosis program, with implications in COPD pathogenesis. Damage-associated molecular patterns released from injured mitochondria and/or necrotic cells may promote proinflammatory and profibrotic responses. In this review, we explore current experimental evidence for mitochondrial dysfunction as a key determinant in the pathogenesis of chronic lung diseases.

Keywords: autophagy; chronic obstructive pulmonary disease; idiopathic pulmonary fibrosis; mitochondrial dysfunction; mitophagy

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Chronic diseases of the lung represent a significant global health burden. Among these, chronic obstructive pulmonary disease (COPD) ranks as a leading cause of mortality worldwide. Exposure to cigarette smoke (CS) is the known primary risk factor for COPD, with potential contributions from domestic or occupational inhalation exposures and environmental air pollution (1). This deadly disease presents with mixed phenotypes of lung tissue destruction

(emphysema), chronic bronchitis, small airway remodeling, and fibrosis, which collectively contribute to lung function impairment (1, 2). In contrast, idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by progressive lung scarring (3). The incidence of IPF is age dependent, affects approximately 3 million people worldwide, and has a high rate of mortality (3). Although the prevalence remains

unclear, a syndrome termed “combined pulmonary fibrosis and emphysema” is characterized by coexisting upper lobe emphysema and lower lobe fibrosis (4).

Although COPD and IPF may share common initiating events (i.e., exposure to CS), the two diseases diverge into drastically different phenotypic endpoints of emphysema and fibrosis, respectively. The cellular and molecular mechanisms

underlying the pathogenesis of COPD remain incompletely delineated, but they include altered protease–antiprotease balance, oxidative stress, and aberrant inflammatory responses to CS (1). Increased expression of transforming growth factor (TGF)- β 1 and activation of its downstream signaling pathways are primary components of IPF and other fibrotic lung diseases, whereas altered TGF- β 1 expression may also contribute to COPD pathogenesis and fibrotic responses associated with COPD (5).

Mitochondria are essential for cellular homeostasis and bioenergetics, whereas mitochondrial dysfunction has emerged as a key determinant in the pathogenesis of human disease (6–8). “Mitochondrial dysfunction” refers to a complex array of cellular events that are initiated by mitochondrial injury incurred by adverse environmental conditions. These include physical changes in mitochondrial morphology, such as swelling and loss of cristae definition, as well as biochemical changes, such as impaired oxidative phosphorylation and energy production, decline in mitochondrial membrane potential, altered metabolic pathways (i.e., fatty acid β -oxidation), increased production of mitochondrial reactive oxygen species (mtROS) (e.g., $O_2^{\cdot -}$ [superoxide anion], H_2O_2), and alterations of intracellular Ca^{2+} flux (6, 7). The production of mtROS and the release of soluble mediators from injured mitochondria may activate downstream processes such as inflammation and cell death (6). The population of mitochondria is maintained by genetically regulated processes that regulate their *de novo* generation (mitochondrial biogenesis) and lysosome-dependent degradation (mitophagy) (9). Mitochondria are also subject to dynamic processes that govern their elongation (fusion) and fragmentation (fission) (9). Furthermore, mitochondria initiate cellular apoptosis via the regulation of Ca^{2+} flux, interactions with the endoplasmic reticulum, and the release of soluble mediators in response to stress stimuli (6). Thus, the processes that govern the abundance, morphology, and turnover of the mitochondria are subject to modulation or deregulation by environmental stress, which in turn may impact the progression of human diseases (7, 8).

Recent studies from our laboratory and others have uncovered significant mitochondrial signatures in chronic lung diseases, which include evidence for aberrant mitochondrial morphology and increased indices of mitochondrial dysfunction in epithelial cells or fibroblasts

(10–16). Perturbations of cellular homeostatic programs associated with mitochondrial dysfunction in chronic lung disease include modulation of the cellular autophagy program, its mitochondria-specific subtype (mitophagy) and associated changes in mitochondrial dynamics (i.e., fusion, fission), and activation of cell death pathways such as apoptosis and necrosis (10–16). In addition, we and others have recently uncovered potential roles for the cellular necroptosis pathway in pulmonary diseases (11, 17). Mitochondrial dysfunction may have differential and cell type-specific functional consequences in different lung cell types (e.g., epithelial cells, fibroblasts, immune cells), which may differentially impact disease progression, leading to divergent outcomes such as the development of fibrosis or emphysema (18). In this article, we review the evidence in human and mouse model studies for mitochondrial dysfunction as a key pathological determinant in two major chronic lung diseases, COPD and IPF.

Mitochondrial Dysfunction as a Pathogenic Component of COPD

Mitochondrial Dysfunction and Cell Death as a Response to CS Exposure

Studies using cultured human pulmonary epithelial cells (e.g., A549, Beas-2B, and primary human lung epithelial cells) have demonstrated mitochondrial injury, dysfunction, and morphological alterations in response to exposure to cigarette smoke extract (CSE) (10–12) (Figure 1). Epithelial cells exposed to CSE displayed dose-dependent loss of adenosine triphosphate production, mitochondrial depolarization (decline in mitochondrial membrane potential), increases in mtROS production, and decline in mitochondrial oxygen consumption (10–12). Similar studies reported loss of mitochondrial electron transport function in response to CSE involving inhibition of complex I and complex II activities (13), as well as pathological accumulation of mitochondrial iron (12). Furthermore, CSE caused changes in mitochondrial morphology consistent with injury in Beas-2B and primary human epithelial cells (11, 12). Evidence for mitochondrial depolarization in lung tissue was demonstrated *in vivo* using a probe for mitochondrial membrane potential (JC-1) in the chronic CS

exposure model in mice (11, 12). Genetic deletion of IRP2 (iron-regulatory protein 2), a COPD susceptibility locus, reduced apparent mitochondrial dysfunction and appearance of mitochondrial abnormalities *in vivo* after chronic CS exposure (12).

Mitochondria are associated with activation of apoptosis through the release of soluble mediators, including cytochrome *c*. Consistent with mitochondrial dysfunction, exposure of cultured epithelial cells to CSE resulted in dose-dependent cytotoxicity associated with activation of apoptosis at low concentrations, followed by impaired apoptosis and increases in necrosis at higher concentrations (10, 11, 13). *In vivo* studies have supported activation of apoptosis in lung tissue in response to chronic CS exposure, including evidence for caspases 8, 9, and 3 activation and enhanced Bax/Bcl-2 ratio in the lung epithelium after chronic CS exposures (14–16).

Functional Roles of Autophagy in Experimental COPD

The autophagy pathway is a cellular homeostatic pathway for the turnover of proteins and damaged organelles, including mitochondria, by autophagosomal sequestration and lysosomal delivery (19). Our prior studies have demonstrated dose-dependent activation of the general autophagy pathway in response to CSE *in vitro* (15), as well as activation in lung tissue in the chronic CS exposure model (15, 16, 20). Evidence for autophagy activation included increased autophagosome numbers and increased LC3B-II (microtubule-associated protein 1 light chain 3B phosphatidylethanolamine conjugate) accumulation, a marker of autophagosome formation, in pulmonary epithelial cells. Genetic knockdown of the major autophagy protein LC3B protected against activation of the extrinsic apoptosis pathway in cultured epithelial cells exposed to CSE (15). These studies suggested a pathological role for autophagy in CS exposure models related to enhanced apoptotic cell death. Genetic studies revealed protective phenotypes for autophagy-deficient mice in response to chronic CS exposure. Mice heterozygous for Beclin-1 (*Becn1*^{+/-}) or deficient in LC3B (*Map1lc3b*^{-/-}) were protected from CS-induced adverse changes in airway function (mucociliary clearance disruption), cilia shortening, and loss of ciliated epithelial cells after CS exposure (20).

Figure 1. Schematic of the proposed pathways whereby mitochondrial dysfunction impacts chronic obstructive pulmonary disease pathogenesis. Exposure to cigarette smoke causes mitochondrial dysfunction, including elevated mitochondrial reactive oxygen species (mtROS) production and mitochondrial depolarization ($-\Delta\psi_m$). Release of mitochondrial damage-associated molecular patterns (DAMPs) may trigger inflammatory and apoptosis pathways. Autophagy and mitophagy activated in response to cigarette smoke exposure may impact various cellular processes that range from protective to maladaptive. These processes include the turnover of ubiquitinated proteins and mitochondria, activation of apoptosis, cilia turnover, activation of the necroptosis pathway, and inhibition of cellular senescence. Epithelial cell injury/cell death may contribute to adverse phenotypes in chronic obstructive pulmonary disease. MLKL = mixed lineage kinase domain-like pseudokinase; mtDNA = mitochondrial DNA; PARK2 = Parkin; PINK1 = phosphatase and tensin homolog-induced putative kinase 1; RIPK3 = receptor interacting protein kinase-3; ROS = reactive oxygen species.

Furthermore, mice deficient in LC3B (*Map1lc3b*^{-/-}) resisted CS-induced lung apoptosis and airspace enlargement after chronic CS exposure (16).

Studies from other laboratories have suggested that CS exposure can induce epithelial cell senescence attributed to impaired autophagy (21–23). Increased polyubiquitinated protein and p62^{SQSTM1} (p62) accumulation in perinuclear aggresomes was observed in CSE-treated pulmonary epithelial cells and in mouse lung tissue after chronic CS exposure. These effects were attributed to dysfunctional autophagy in response to CS resulting in reduced aggresome clearance and were similar to that observed in aged mice (22, 23). The autophagy-stimulating antioxidant compound cysteamine reduced aggresomal accumulation of p62 and ubiquitinated protein, inhibited apoptosis and cellular senescence in response to CS/CSE exposure *in vitro* and *in vivo*, and improved bacterial clearance in a *Pseudomonas aeruginosa*-induced exacerbation model (23). Similar studies identified transcription factor EB, which is sequestered in aggresomes after CS exposure, as a potential

pharmacological target for restoration of autophagy decline (24).

Taken together, these studies point to controversy in the literature with regard to the regulation and function of autophagic pathway modulation in response to CS exposure in model studies. Genetic validation studies implicated select autophagic proteins (i.e., Beclin-1 and LC3B) as having proapoptotic effects in CS-induced responses, whereas it is noted that individual proteins may have signaling roles beyond regulation of the autophagy pathway. Careful evaluation of differential experimental conditions between studies, as well as further experiments aimed at detecting autophagic activity in various lung cell types during CS exposure or during the progression of COPD, may resolve the discrepancies. However, it remains clear that autophagy deregulation is an important component of toxic responses to CS exposure, which may vary in a cell type- and model-specific fashion.

Functional Roles of Mitophagy in Experimental COPD

A selective form of autophagy, termed “mitophagy,” facilitates the turnover of

dysfunctional mitochondria. In the classical pathway, the mitophagy regulator protein PINK1 (phosphatase and tensin homolog-induced putative kinase 1), a serine/threonine kinase, is constitutively degraded on the inner mitochondrial membrane. In response to loss of mitochondrial membrane potential, PINK1 accumulates on the outer mitochondrial membrane, resulting in the recruitment of Parkin, an E3 ubiquitin ligase. Parkin ubiquitinates damaged mitochondria for recognition by p62^{SQSTM1} and subsequent autophagosomal assimilation (25). Recent studies suggest that PINK1 may exert mitophagy-independent cellular functions in addition to Parkin activation and is also dispensable for basal mitophagy in metabolically active tissues (26, 27).

Activation of the mitochondrial fission pathway regulated by DRP1 (dynamin-1-like protein) may represent a functional cellular precursor pathway to mitophagy. CS exposure induced mitophagy in pulmonary epithelial cells via depolarization of mitochondria and stabilization of PINK1 (11). CSE exposure caused dose-dependent

increases in PINK1 expression and DRP1 phosphorylation, which were dependent on mitochondrial dysfunction and upregulation of mtROS because these events were abrogated by the mitochondria-targeted antioxidant MitoTEMPO (11). PINK1-deficient mice were protected against mitochondrial dysfunction, airspace enlargement, and airway dysfunction during CS exposure *in vivo* (11). These studies suggest that CS-induced autophagy and selective autophagy (i.e., PINK1-dependent mitophagy) exert a proathogenic function in CS-induced airway dysfunction and airspace enlargement in mice.

We have also uncovered potential roles for necroptosis, a cellular program regulated by RIPK1 (receptor-interacting protein kinase 1) and RIPK3, and MLKL (mixed lineage kinase domain-like pseudokinase) in chronic lung disease (11). Our studies revealed that a component of CS-induced necrotic cell death *in vitro* is represented by the programmed necrosis (necroptosis) pathway because it is sensitive to the RIPK1 inhibitor necrostatin 1 (11). Activation of mitophagy in epithelial cells was associated with downstream activation of the cellular necroptosis pathway and upregulation of RIPK3. The regulation of RIPK3 was dependent on PINK1, as validated by genetic interference or deletion studies *in vitro* and *in vivo* (11). Furthermore, the chemical inhibitor of mitochondrial division/mitophagy Mdivi-1 (mitochondrial division inhibitor 1) protected against CS-induced mitochondrial dysfunction and necroptotic cell death (11). In support of these findings, application of the necroptosis inhibitor necrostatin 1 inhibited neutrophilic airway inflammation in CS-exposed mice (17). In contrast, knockdown of either PINK1 or Parkin (PARK2), which inhibited mitophagy and increased mtROS production, resulted in increased cellular senescence in CS-exposed primary human bronchial epithelial cells, indicating a protective role for these proteins (28). The reasons for these discrepancies between studies remain unclear at present, although collectively they demonstrate crucial roles for PINK1 in determining cell fate in response to CS exposure.

Mitochondrial Dysfunction and Mitophagy in Human COPD

Potential roles of autophagy and mitophagy in human COPD have been suggested by

studies using human tissues derived from patients with COPD. For example, increased abundance of autophagosomes and increased expression and activation of LC3B were observed in human lung tissues from patients with advanced COPD (15, 16). We have observed elevated expression of PINK1 in epithelial cells in emphysematous regions of human lung. Enhanced PINK1 expression in COPD lung tissue coincided with increased expression of the necroptosis protein RIPK3 (11). Increased p62 accumulation and decreases in Parkin expression were observed in the lungs of patients with advanced COPD, which were attributed to autophagy/mitophagy impairment (22, 28). A state of impaired autophagy was also described in the alveolar macrophages isolated from human smokers and in CS-exposed macrophages (29). These observations suggest that smokers may be susceptible to respiratory infections due to defective bacterial clearance by macrophage autophagy. Furthermore, an aberrant and deleterious mitochondrial phenotype has been described in the skeletal muscle of patients with COPD, relative to control patients, which includes mitochondrial functional alterations, reduced mitochondrial density, altered respiratory function, and increased mtROS production (30). Further studies will be needed to define the precise roles of mitochondrial decline, autophagy, and mitophagy in human COPD not only in the lung but also in other organs potentially impacted in COPD, such as muscle and kidney.

Mitochondrial Dysfunction as a Pathogenic Component of IPF

Mitochondrial Dysfunction and Autophagy/Mitophagy as Pathogenic Mediators of Fibrosis: Evidence from *In Vitro* and *In Vivo* Studies

Recent model studies highlight differential and cell type-specific roles for mitochondrial dysfunction, autophagy, and mitophagy in the pathogenesis of fibrotic lung disease (Figure 2). TGF- β 1, via stimulation of its downstream effector pathways, is a primary activator of fibrogenic responses. *In vitro* studies have revealed that application of TGF- β 1 in lung epithelial cells induced mitochondrial depolarization, mtROS production, and expression of PINK1 and phosphorylated

Drp1 (31). These events were abrogated by mtROS scavenging using mitochondria-targeted antioxidants (MitoTEMPO). Increased mitophagy was demonstrated by increased LC3B and PINK1 colocalization after TGF- β 1 exposure (31). Knockdown of PINK1 expression in lung epithelial cells promoted TGF- β 1-induced cell death (31). These experiments suggest that TGF- β 1 can activate the mitophagy program in epithelial cells in association with counterregulatory and antifibrotic effects. Epithelial cells derived from *Pink1*^{-/-} mice revealed enhanced reactive oxygen species production and cell death in response to TGF- β 1, confirming a protective role for PINK1 against TGF- β 1-dependent responses. Knockdown of PINK1 expression in lung epithelial cells also resulted in mitochondrial depolarization and expression of profibrotic factors (32).

In cultured fibroblasts, knockdown of Parkin was more effective than knockdown of PINK1 in enhancing myofibroblast differentiation and proliferation through a mechanism involving activation of the platelet-derived growth factor receptor/phosphoinositide 3-kinase/AKT signaling pathway in a reactive oxygen species-dependent fashion (33). The authors concluded that Parkin was the dominant factor in regulating fibroblast phenotypes in IPF (33).

Fibroblasts isolated from human patients with IPF displayed reduced autophagy associated with elevated activation of mammalian target of rapamycin and decreased activity of the energy-sensing kinase adenosine monophosphate-activated protein kinase (AMPK) (34). AMPK-activating compounds were found to inhibit profibrotic responses in TGF- β 1-stimulated fibroblasts, as well as to stimulate mitochondrial biogenesis and restore fibroblast sensitivity to apoptosis. In contrast, epithelial cells isolated from patients with IPF were characterized by normal autophagy and high AMPK activation. These studies implicated an autophagy-deficient phenotype in IPF being selectively localized to fibroblasts (34).

In the mouse model of bleomycin-induced pulmonary fibrosis, activation of autophagy by application of rapamycin reduced collagen deposition (35). Similarly, pharmacological application of the AMPK activator metformin, which induces autophagy, resulted in the inhibition of

Figure 2. Schematic of the proposed pathways whereby mitochondrial dysfunction impacts idiopathic pulmonary fibrosis (IPF) pathogenesis. Exposure to profibrotic stimuli, such as transforming growth factor (TGF)- β 1, causes mitochondrial dysfunction, including elevated mitochondrial reactive oxygen species (mtROS) production and mitochondrial depolarization ($-\Delta\psi_m$). Release of mitochondrial damage-associated molecular patterns (DAMPs) such as mitochondrial DNA (mtDNA) may trigger profibrotic pathways. IPF has been described as a disease associated with impaired autophagy. Activation or stimulation of autophagy and mitophagy may play a protective role in IPF pathogenesis. Mitophagy may exert protective functions, including the removal of dysfunctional mitochondria; the inhibition of cellular senescence; and the inhibition of profibrotic processes, including extracellular matrix (ECM) deposition and myofibroblast differentiation. ER = endoplasmic reticulum; PARK2 = Parkin; PINK1 = phosphatase and tensin homolog-induced putative kinase 1; ROS = reactive oxygen species.

established pulmonary fibrosis in the bleomycin model (34).

Mitophagy-deficient *Pink1*^{-/-} mice were more susceptible than control mice to bleomycin-induced lung fibrosis, as well as virus-induced fibrosis (MHV68 model), indicative of a protective role for PINK1 against fibrogenesis (31, 32). These differences were attributed to increased pulmonary apoptosis in *Pink1*^{-/-} mice subjected to the MHV68 model but not the bleomycin model (31, 32). *Park2*^{-/-} mice were susceptible to bleomycin-induced fibrosis, and this phenotype was ameliorated by antioxidant supplementation (33).

A functional link between endoplasmic reticulum stress pathways, mitochondrial dysfunction, and PINK1-dependent mitophagy was recently described in pulmonary fibrosis (36). ATF3 (activating transcription factor 3) was identified as a negative regulator of PINK1 gene expression via binding to a regulatory element in the proximal promoter region of the *Pink1* gene. Overexpression of ATF3 in epithelial cells resulted in accumulation of depolarized mitochondria, increased mtROS production, and loss of cell viability. In contrast to the observed phenotype of *Pink1*^{-/-} mice, mice genetically deficient

in ATF3 in type II epithelial cells were protected against bleomycin-induced pulmonary fibrosis (36).

Functional Roles of Autophagy/ Mitophagy in Human IPF

Recent ultrastructural studies have revealed an increased number of mitochondria with swollen appearance or damaged cristae in IPF lung samples when compared with control lung samples (31, 32). The studies of Bueno and colleagues also described a pronounced increase in mitochondrial content in alveolar type II epithelial cells in highly fibrotic areas of human IPF lungs (32). Cells with increased positivity for the mitochondrial marker TOM20 (translocase of outer membrane 20) also showed increased expression of the endoplasmic reticulum stress marker BiP (binding immunoglobulin protein; GRP78 [78 kD glucose-regulated protein]), suggesting an association of increased mitochondrial content with increased endoplasmic reticulum stress in alveolar epithelial cells from patients with IPF (32).

Studies from our laboratory revealed that lung tissues from patients with IPF were deficient in autophagy as assessed by LC3B-II expression and absence of detectable

autophagosomes (35). The activation of AMPK, as determined by the levels of phosphorylated AMPK, was found to be reduced in myofibroblast foci, consistent with autophagy impairment (34).

Bueno and colleagues, using gene expression profiling, described significant downregulation of *PINK1* gene expression in lung samples from patients with IPF (32). These authors also reported accumulation of ATF3, a negative transcriptional regulator of PINK1, in aged or IPF lung tissue (36). In contrast, Patel and colleagues reported increased PINK1 expression in IPF lung tissue by immunofluorescence associated with increased numbers of damaged mitochondria (31). The reason for these discrepancies in reported PINK1 expression in IPF remain unclear; however, both groups reported a susceptibility phenotype of *Pink1*^{-/-} mice in bleomycin-induced lung fibrosis, supportive of an antifibrotic role for PINK1 in experimental models. Human IPF lung displayed reduced PARK2 (Parkin) expression in association with upregulated platelet-derived growth factor receptor phosphorylation (33). The latter study related these changes to mitophagy impairment and increased myofibroblast differentiation in IPF (33).

These studies implicate mitophagy as a protective mechanism in pulmonary fibrosis.

Role of Mitochondrial Damage-associated Molecular Patterns in Chronic Lung Disease

Damage-associated molecular patterns (DAMPs), molecules generated and released by cellular injury, can propagate inflammatory responses. DAMPs can trigger innate immune responses by activating pattern recognition receptors. Recent studies have demonstrated that cellular DAMPs released by CS exposure from necrotic epithelial cells or neutrophils can stimulate proinflammatory cytokine and/or chemokine (e.g., interleukin 6, chemokine [C-X-C motif] ligand 8) production in target epithelial cells and can trigger neutrophil recruitment and inflammation *in vivo* (17, 37). Mitochondria-associated DAMPs include mitochondrial DNA (mtDNA), which is released from mitochondria in response to mitochondrial depolarization and mtROS production (38). mtDNA can act as a cellular DAMP to activate macrophage inflammatory pathways, including the NLRP3 (NACHT, LRR and PYD domains-

containing protein 3) inflammasome pathway leading to caspase 1 activation and maturation of proinflammatory cytokines (38). Previous work from this laboratory has also demonstrated that increased mtDNA in the plasma correlated with mortality of sepsis and sepsis-associated acute respiratory distress syndrome (39). These associations are currently less well defined for chronic lung diseases. Recent studies, however, have demonstrated that mtDNA levels in bronchoalveolar lavage fluid and plasma are increased in IPF and that increased plasma mtDNA levels are associated with more disease progression and higher mortality in patients with IPF (40). mtDNA was identified as a proinflammatory and profibrotic factor in normal human lung fibroblasts, such that exposure to exogenous mtDNA promoted α -smooth muscle actin expression (40). Ongoing studies in this laboratory and others will assess the significance of mtDNA release in other chronic lung diseases, such as COPD.

Conclusions

Accumulating evidence demonstrates that mitochondrial dysfunction can act as a key mediator of the pathogenesis of many

diseases, including human chronic parenchymal lung diseases. Mitochondrial autophagy (mitophagy), activated in response to mitochondrial injury incurred by noxious stimuli, plays a complex role in the lung, where it can have both protective and injurious effects on the progression of lung disease. Recent observations indicate that the differential effects of autophagy/mitophagy in pulmonary disease are cell type specific. PINK1-dependent mitophagy and the autophagy pathway in general were found to be proinflammatory in COPD models and protective in IPF models, which may reflect the opposing nature of the two diseases. Mitochondrial DAMPs, including mtDNA released into the systemic circulation, have been correlated to mortality in diseases such as sepsis and IPF, though a signature in COPD remains unclear. The significance of mitochondrial DAMPs in chronic lung diseases remains unclear and remains an active area of investigation. Further research is needed to design intervention strategies to ameliorate mitochondrial dysfunction and furthermore to target the autophagy and mitophagy pathways as valid therapeutic approaches in chronic lung diseases. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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