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REVIEW ARTICLE

Mitochondrial dysfunction in inflammatory responses and cellular senescence: pathogenesis and pharmacological targets for chronic lung diseases

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Mitochondria are dynamic organelles, which couple the various cellular processes that regulate metabolism, cell proliferation and survival. Environmental stress can cause mitochondrial dysfunction and dynamic changes including reduced mitochondrial biogenesis, oxidative phosphorylation and ATP production, as well as mitophagy impairment, which leads to increased ROS, inflammatory responses and cellular senescence. Oxidative stress, inflammation and cellular senescence all have important roles in the pathogenesis of chronic lung diseases, such as chronic obstructive pulmonary disease, pulmonary fibrosis and bronchopulmonary dysplasia. In this review, we discuss the current state on how mitochondrial dysfunction affects inflammatory responses and cellular senescence, the mechanisms of mitochondrial dysfunction underlying the pathogenesis of chronic lung diseases and the potential of mitochondrial transfer and replacement as treatments for these diseases.

Abbreviations

AMPK, AMP-activated protein kinase; α-SMA, α-smooth muscle actin; BPD, bronchopulmonary dysplasia; COPD, chronic obstructive pulmonary disease; DRP1, DNM1L, dynamin 1-like; $\Delta\psi m$, mitochondrial membrane potential; ETC, electron transport chain; FIS1, fission 1; MDVs, mitochondria-derived vesicles; Mfn, mitofusin; MiDAS, mitochondrial dysfunction-associated senescence; MPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; mtROS, mitochondrial ROS; $O_2^{\cdot-}$, superoxide anion; OPA1, optic atrophy 1; PINK1, PTEN-induced putative kinase 1; SASP, senescence-associated secretory phenotype; UCP, mitochondrial uncoupling protein

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Tables of Links

TARGETS	
Other protein targets[a]	**Enzymes**[d]
TNF	AMPK
GPCRs[b]	PINK1
CXCR2	SIRT1
P2Y receptors	**Transporters**[e]
Catalytic receptors[c]	UCP
PRRs	
TNFRs	

LIGANDS	
ATP	IL-8
IL-1β	TGF-β1
IL-6	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

Mitochondria are highly dynamic organelles which contain outer and inner membranes that separate the intermembrane space and matrix. The inner membrane is folded many times and it is these folds that are known as the cristae, which harbors the electron transport chain (ETC) that contains five multiprotein complexes named complex I–V. Mitochondria act as a cytosolic calcium reservoir, and mitochondrial calcium regulates ATP synthesis (Tarasov *et al.*, 2012). However, calcium overload in the mitochondrial matrix enhances the generation of mitochondrial ROS (mtROS) and the release of cytochrome c, resulting in apoptosis and cell death (Brookes *et al.*, 2004; Finkel *et al.*, 2015). Sustained levels of ROS cause the oxidation of DNA, lipid and protein, which play important roles in the pathogenesis of chronic lung diseases. However, moderate levels of mtROS act as a physiological signal to protect against the adverse effects of various cellular stresses and infection (West *et al.*, 2011; Al-Mehdi *et al.*, 2012; Katz *et al.*, 2014). For instance, suppression of perinuclear mitochondrial clustering reduces mtROS-mediated vascular endothelial growth factor gene transcription in response to hypoxia (Al-Mehdi *et al.*, 2012). Therefore, mtROS is a double-edged sword with regard to the regulation of cell function (Sena and Chandel, 2012; Kalogeris *et al.*, 2014).

Mitochondria are considered to be the powerhouse of the cell as they have the ability to generate ATP through oxidative phosphorylation (Figure 1); this provides the energy for cell survival and functions. Also, there is accumulating evidence that the mitochondria has a non-energetic role in regulating metabolism, apoptosis, innate immunity, inflammatory responses and aging (Nunnari and Suomalainen, 2012; Friedman and Nunnari, 2014). All of these processes are involved in the pathogenesis of chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and bronchopulmonary dysplasia (BPD). In this review, we focus on how the dysfunction of mitochondria can affect inflammatory responses and cellular senescence, as well as their involvement in the development of chronic lung diseases and their co-morbidities.

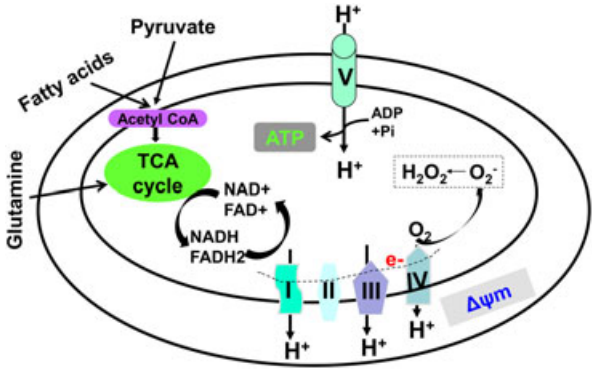

Figure 1

Tricarboxylic acid (TCA) cycle and oxidative phosphorylation. ATP generation starts in the TCA cycle and ends with oxidative phosphorylation. During the TCA cycle, NADH and FADH2 are generated, which are oxidized to provide electrons through the ETC. Mitochondrial O_2^- is produced when oxygen molecules gain electrons leaked from the ETC. Through oxidative phosphorylation, free energy is used to pump protons out of the matrix, forming $\Delta\psi m$, which ultimately provides the energy needed to generate ATP.

Mitochondrial dynamics and quality control

Upon stress, mitochondria develop a protective mechanism to control and maintain their quality (Figure 2). This starts as mitochondrial biogenesis, which is the growth and division of pre-existing mitochondria rather than *de novo* synthesis. Once stressed, mitochondria fuse together so as to separate the healthy and damaged/stress mitochondria through a fission mechanism. At the molecular level, both dynamin 1-like (DNM1L or DRP1) and fission 1 (FIS1) regulate mitochondrial fission, while optic atrophy 1 (OPA1) and mitofusin 1 and 2 (Mfn1 and Mfn2) modulate the fusion process. Healthy mitochondria enter the mitochondrial life cycle to produce energy and take part in cell signalling, whereas damaged mitochondria are mainly degraded via the

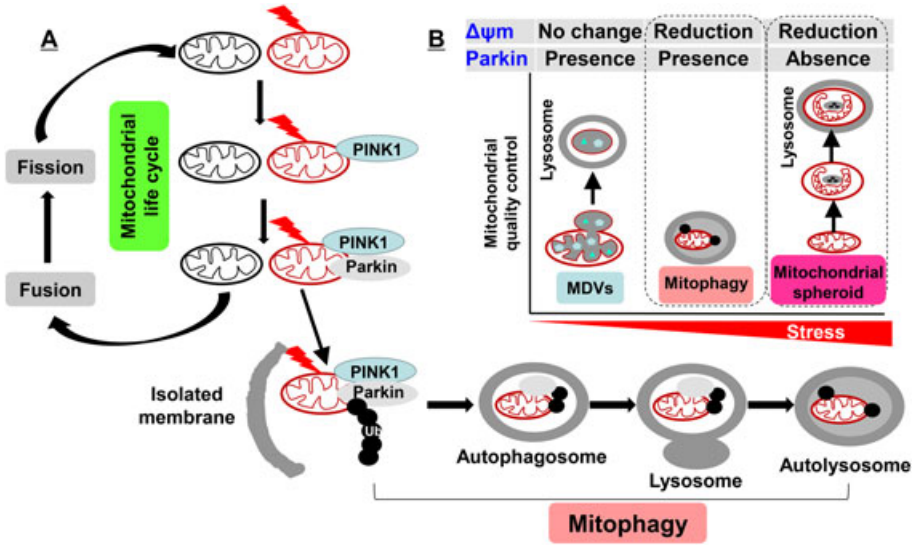

Figure 2

Mitochondrial quality control. (A) Once mitochondria encounter stress and the Δψm is reduced, damaged mitochondria are separated, and Pink1 is recruited into the mitochondrial out membrane. This leads to the translocation of Parkin to mitochondria, which triggers the ubiquitination of mitochondrial proteins including Mfns. Finally, autophagosomes enclose damaged mitochondria and fuse with lysosome for degradation. The intact mitochondria enter the mitochondrial life cycle through fusion and fission for biogenesis. (B) There are several approaches for mitochondrial quality control, including MDVs, mitophagy and mitochondrial spheroid formation. Based on the requirement of Δψm reduction and Parkin recruitment, we surmise that MDVs, mitophagy and mitochondrial spheroid formation are employed in different degrees of mitochondrial stress.

mitochondrial autophagy (mitophagy) pathway (Youle and Narendra, 2011; Ashrafi and Schwarz, 2013). The timely elimination of damaged, dysfunctional and aged mitochondria plays a crucial a role in preventing the release of pro-apoptotic proteins, mtROS and mitochondrial DNA (mtDNA), which cause apoptosis and inflammasome activation (Kepp *et al.*, 2011; Nakahira *et al.*, 2011; Zhou *et al.*, 2011; Shimada *et al.*, 2012; Alfonso-Loeches *et al.*, 2014).

Mitophagy is initiated when the mitochondrial membrane potential (Δψm) is reduced by mild stress. This causes the recruitment of a PTEN-induced putative kinase 1 (PINK1) on the mitochondrial out membrane, which further recruits and phosphorylates an E3 ubiquitin ligase, Parkin, from the cytosol (Springer and Kahle, 2011; Vincow *et al.*, 2013). The phosphorylated Parkin (Ser^{65}) triggers the ubiquitination and degradation of mitochondrial proteins including Mfn1 and Mfn2, hence preventing mitochondrial fusion. This triggers the translocation of damaged mitochondria on the isolated membranes containing microtubule-associated protein light chain 3, leading to the formation of autophagosomes, which finally fuse with lysosomes leading to the clearance of damaged mitochondria from the cells (Youle and Narendra, 2011; Hattori *et al.*, 2014). However, recent studies have reported Smurf1- and Mul1-dependent mitophagy, which is independent of Parkin (Orvedahl *et al.*, 2011; Lokireddy *et al.*, 2012; Fu *et al.*, 2013; Chen *et al.*, 2014). Therefore, further investigations on Parkin-dependent and -independent mitophagy would enhance the understanding of mitochondrial biology and pathophysiology of mitochondrial dysfunction-associated diseases. However, the approaches used to detect mitophagy *in vivo* are limited. Traditional methods such as electronic microscopy are able to capture and determine the mitochondrial components or remnants within the autophagosome (Zhu *et al.*, 2011). However, these methods are not quantitative as they only measure a small fraction of cell and tissue. Keima is a coral-derived protein that has pH-dependent fluorescent properties, which allows the determination of its localization in mitochondria (pH ~8.0) or lysosome (pH ~4.5). A newly developed transgenic mouse model, in which a mitochondrial-targeted form of the fluorescent reporter Keima is overexpressed, provides a real-time monitor of mitophagy *in vivo* (Sun *et al.*, 2015).

Recent studies have shown that mitochondria-derived vesicles (MDVs) can be formed as an alternative pathway for mitochondrial quality control. MDVs carry the oxidized mitochondrial proteins and lipids into peroxisomes or fuse with endosomes, which are finally degraded by lysosome, and this process is independent of a reduction in the Δψm or mitophagy (Soubannier *et al.*, 2012a; Du Toit, 2014; Sugiura *et al.*, 2014). In other words, MDVs can occur in cells with an intact mitochondrial network with no reduction in the Δψm. It is interesting to note that MDVs do not contain the mitochondrial ETC or nucleoids (Soubannier *et al.*, 2012b), which suggests the constituents of MDVs are specific. Both PINK1 and Parkin have been shown to involved in the biogenesis of MDVs (McLelland *et al.*, 2014; Sugiura *et al.*, 2014). However, how PINK1 and Parkin have differential effects on mitophagy and MDV formation remains to be determined.

Mitochondrial spheroid formation is a reversible process, which has also been shown to control mitochondrial quality and can be induced *in vivo* in the liver by acetaminophen-mediated severe oxidative mitochondrial damage in the absence of Parkin (Ding *et al.*, 2012; Ni *et al.*, 2013; Cook *et al.*, 2014; Ding and Eskelinen, 2014). In contrast to mitophagy or MDVs, Parkin suppresses mitochondrial spheroid

formation by ubiquitin and degradation of Mfn, whereas Mfn promotes the formation of mitochondrial spheroids (Ding *et al.*, 2012). Overall, we surmise that mitochondria will employ either MDVs, mitophagy or spheroid formation according to the extent of their damage (from mild to severe) to maintain their homoeostasis (Figure 2). Further studies are required to determine the regulation, interaction and crosstalk among mitophagy, MDVs and mitochondrial spheroids needed to maintain mitochondrial quality control under stress conditions.

Mitochondrial dysfunction in inflammation

Mitochondrial dysfunction is linked to inflammatory responses (Lopez-Armada *et al.*, 2013). Accumulating evidence shows that increased mtROS generation, extracellular ATP and mtDNA release cause inflammatory responses, which, in turn, aggravate mitochondrial dysfunction (Figure 3).

mtROS are generated during the transportation of electrons provided by the oxidation of NADH and FADH2 produced during the tricarboxylic acid cycle. The main site of electron leakage is the complex I (NADH dehydrogenase), which oxidizes oxygen to generate superoxide anion ($O_2^{\cdot-}$). There is approximately 0.2%–2% oxygen consumed during oxidative phosphorylation generating $O_2^{\cdot-}$, which is further dismutated into hydrogen peroxide (H_2O_2). Due to the difference in their electrophilic and electrophobic properties as well as their half-life, the concentrations of H_2O_2 in mitochondria are 100 times greater than that of $O2^{\cdot-}$ (Cadenas and Davies, 2000; Li *et al.*, 2013). This makes mitochondrial H_2O_2 an ideal signalling molecule in cells (Al-Mehdi *et al.*, 2012), whereas $O2^{\cdot-}$ causes oxidative stress leading to DNA damage and an impairment of mitochondrial integrity through the generation of peroxynitrite within mitochondria. Under severe mitochondrial damage, high amounts of mtROS are generated which causes deleterious effects including abnormal inflammatory responses (Bulua *et al.*, 2011; Naik and Dixit, 2011). There are several mechanisms for mtROS-mediated inflammatory responses, including RIG-I-like receptors, MAPK, TNFRs and NLRP3 inflammasome signals (Emre *et al.*, 2007; Tal *et al.*, 2009; Bulua *et al.*, 2011; Zhou *et al.*, 2011). This is reflected by the findings that inhibition of mtROS production reduces the release of pro-inflammatory mediators including IL-6 and TNF in cells from patients with TNFR1-associated periodic syndrome (Bulua *et al.*, 2011). A separate study demonstrated that NLRP3 deletion abolishes mtROS elevation-induced IL-1β expression (Zhou *et al.*, 2011). Mitochondrial uncoupling is a physiological process that dissipates the proton gradient, which allows protons to bypass ATP synthase. Mitochondrial uncoupling is modulated by uncoupling proteins (UCPs) located in the mitochondrial inner membrane. Mild mitochondrial uncoupling significantly reduces mtROS generation, thereby decreasing inflammatory responses (Lee *et al.*, 2005; Toime and Brand, 2010; Romaschenko *et al.*, 2015).

There are three mechanisms for ATP release: (i) vesicular (exocytotic) release; (ii) diffusion through membrane pores or damaged membranes; and (iii) active transport, which

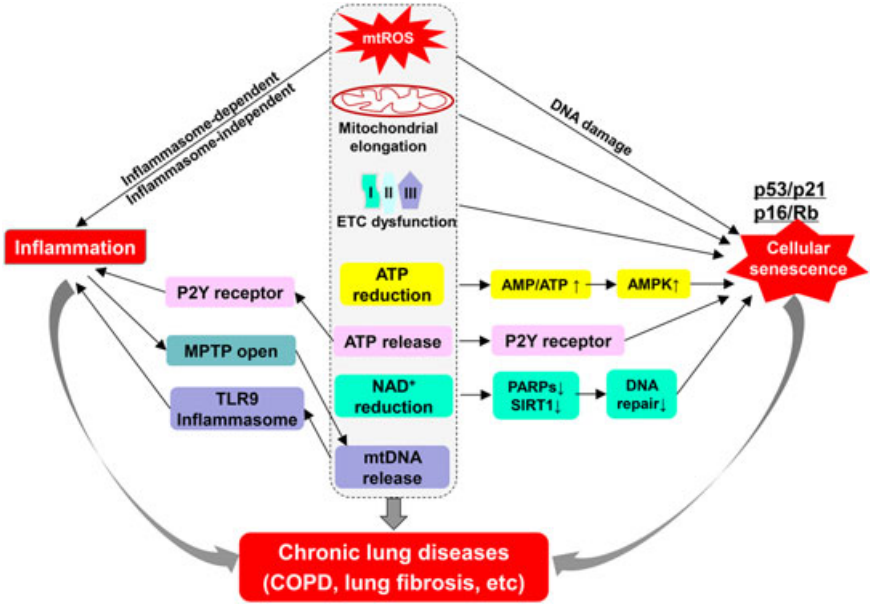

Figure 3

Mitochondrial dysfunction in inflammatory responses and cellular senescence. Abnormal changes in mitochondrial morphology and function play pivotal roles in stress-induced inflammatory responses and cellular senescence. Increased mtROS, mitochondrial elongation and impaired oxidative phosphorylation cause cell cycle arrest and cellular senescence. ATP and NAD^+ reduction due to dysfunctional oxidative respiration also result in cellular senescence by regulating AMPK, sirtuin1 and PARPs. Meanwhile, mtROS, extracellular ATP and mtDNA can cause inflammatory responses in inflammasome-dependent or independent manners. Inflammation is able to induce the opening of MPTP, leading to mtDNA release from mitochondria. Both cellular senescence and inflammatory responses participate in the pathogenesis of chronic lung diseases.

occurs in a variety of cells including neurons, epithelial cells, fibroblasts, macrophages and neutrophils (Fitz, 2007). Released ATP regulates cell functions by activating purine receptors (P2X and P2Y) in the plasma membrane in an autocrine and paracrine manner. A persistent increase in extracellular ATP serves as a danger signal is associated with the development of inflammation and cell death (Riteau *et al.*, 2010, 2011). It has been shown that activation of purine receptors results in the generation of ROS, chemokines and pro-inflammatory mediators (Bours *et al.*, 2011; Cauwels *et al.*, 2014). Additionally, inflammasome is involved in extracellular ATP-mediated aseptic inflammation (Iyer *et al.*, 2009; Weber *et al.*, 2010, 2013). Therefore, the blockade of purine receptors may represent a potential therapeutic for abnormal inflammatory responses to extracellular ATP.

The mitochondrion has its own circular DNA, like bacterial DNA, which encodes 13 polypeptide subunits essential for the oxidative phosphorylation, 22 tRNAs and 2 rRNAs. Recent studies have shown that mtDNA can be released into cytosol or the circulation. It then acts as mitochondrial damage-associated molecular patterns (DAMPs) in inducing activation of inflammasome (Kepp *et al.*, 2011; Nakahira *et al.*, 2011; Oka *et al.*, 2012; Shimada *et al.*, 2012) or engages the DNA sensor cGMP–AMP synthase promoting interferon responses and viral resistance (West *et al.*, 2015). Further studies have revealed that oxidized mtDNA is the actual element that binds and activates the NLRP3 inflammasome (Shimada *et al.*, 2012). mtDNA digestion by DNase II protects against tissue inflammation, while IL-1β production is significantly reduced in macrophages lacking mtDNA (Shimada *et al.*, 2012, 2013). The mechanisms underlying mtDNA-mediated inflammasome activation are associated with the cell-autonomous activation of specific pattern recognition receptors such as TLR9 (Oka *et al.*, 2012). One of the mechanisms for mtDNA release is the formation of exosomes and the opening of the mitochondrial permeability transition pore (MPTP) (Patrushev *et al.*, 2004, 2010). It should be noted that inflammation itself induces the opening of MPTP. This is demonstrated by the findings that the pro-inflammatory cytokines, including TNF-α, IFN-γ and IL-17, cause the opening of MPTP in human conjunctival epithelial cells and platelets (Gao *et al.*, 2013; Yuan *et al.*, 2015). Cyclosporine A, an MPTP inhibitor, prevents mtDNA release (Gao *et al.*, 2013). Hence, MPTP serves as a checkpoint to determine the fate of cells. These findings suggest a robust feedback exists between mtDNA and inflammatory responses, and inhibition of exosome formation and MPTP would protect against mtDNA release-induced inflammatory responses.

Mitochondrial dysfunction in cellular senescence

Cellular senescence is a status of irreversible growth arrest, which is a biological term for aging. There are two p53/p21^{cip1} and p16^{INK4}/Rb pathways that mediate cellular senescence. According to the mitochondrial free radical theory of aging, mitochondrial stress is considered as an inducer of cellular senescence whereas mtROS is the factor most studied factor through persistent DNA damage (Figure 3). Scavenging mtROS with the mitochondria-targeted antioxidant MitoQ or acetyl-L-carnitine delays replicative senescence and/or stress-induced premature senescence (Saretzki *et al.*, 2003; Wu *et al.*, 2014). Furthermore, replicative senescence of human fibroblasts is delayed by mild mitochondrial uncoupling, which is associated with reduced production of mtROS (Passos *et al.*, 2007). However, overproduction of UCP2 causes senescent-like morphology in a kidney fibroblast cell line (Nishio and Ma, 2016), suggesting the existance of mtROS-independent cellular senescence. Controversial studies have suggested that mtROS increase is just a consequence of cellular senescence. High levels of oxidative damage to mtDNA are observed in the longest-living rodent, the naked mole rat (Andziak *et al.*, 2006). Additionally, overexpression of mitochondrial SOD2 and catalase are not sufficient to block stress-induced cellular senescence (Klimova *et al.*, 2009; Lawless *et al.*, 2012). Nevertheless, whether mtROS triggers cellular senescence independently of its role in inducing oxidative damage is still not known.

Abnormal alterations in mitochondrial dynamics affects mitochondria, leading to cellular senescence (Figure 3). Genetic disruption of membrane-associated ring finger C3HC4 5 (MARCH5), a mitochondrial E3 ubiquitin ligase, induces cellular senescence by blocking DRP1 activity and causing mitochondrial elongation (Park *et al.*, 2010). This is in agreement with our findings that mitochondria are elongated during smoke stress-induced senescence in lung epithelial cells and fibroblasts (Ahmad *et al.*, 2015). In contrast, depletion of both hFIS1 and OPA1 leads to extensive mitochondrial fragmentation and significantly protects against senescence-associated phenotypic changes (Lee *et al.*, 2007). These findings indicate that mitochondrial elongation promotes cell cycle arrest and subsequent senescence, which is associated with reduced $\Delta\psi m$, increased mtROS and DNA damage. We and others have shown that mitophagy impairment triggers stress-induced cellular senescence (Ahmad *et al.*, 2015; Ito *et al.*, 2015). This may be due to the reduction in PINK1 and Parkin levels, as knockdown of PINK1 or Parkin enhances smoke stress-induced premature senescence. Further investigations are required to determine how impairment of PINK1/Parkin-dependent mitophagy up-regulates p53- and p16-dependent cellular senescence.

Mitochondrial dysfunction decreases ATP synthesis, which induces cellular senescence (Figure 3). The mechanism underlying this involves AMP-activated protein kinase (AMPK) activation via increased AMP (or ADP) to ATP ratio. Indeed, AMPK directly up-regulates p53 and p16 at the transcription and post-translational levels leading to cellular senescence (Wang *et al.*, 2003, 2013). AMPK has been shown to up-regulate sirtuin1, an anti-aging/senescence molecule, by augmenting mitochondrial metabolite NAD^+ levels (Canto *et al.*, 2009). However, under conditions of mitochondrial stress, complex I is not capable of oxidizing the NADH into NAD^+, which may provoke AMPK to induce cellular senescence.

Link between inflammation and senescence in chronic lung diseases

During proliferation arrest, senescence cells are metabolically active and are more likely to secrete inflammatory mediators such as IL-1, IL-6, IL-8 and MMPs. This phenomenon is termed senescence-associated secretory phenotype (SASP). The

mechanisms underlying SASP are associated with activation of p38 MAPK and NF-κB (Chien *et al.*, 2011; Freund *et al.*, 2011). In turn, these SASP mediators can reinforce senescence in neighbouring cells through CXCR2 receptors (Acosta *et al.*, 2008). This is evident from findings showing that NF-κB inhibition delays cellular senescence (Tilstra *et al.*, 2012). Interestingly, mitochondrial defects also trigger proliferation of neighbouring cells via a SASP in *Drosophila* (Nakamura *et al.*, 2014). Hence, the SASP mediators from senescent cells may have different components, which pose differential influences on neighbouring cells, such as senescence, proliferation or differentiation. Indeed, a recent study has shown that mitochondrial dysfunction-associated senescence (MiDAS) exhibits a modified SASP that lacks the IL-1-dependent inflammatory arm but shows high levels of the anti-inflammatory cytokine IL-10 (Wiley *et al.*, 2016). Further studies on SASP components from senescent epithelial cells, fibroblasts and inflammatory cells along with mitochondrial function may reveal the role of mitochondria in diverse paracrine effects of SASP.

Both senescence and inflammatory responses play important roles in the pathogenesis of chronic lung diseases including COPD and lung fibrosis, which we and others have extensively discussed (Aoshiba and Nagai, 2009; MacNee and Tuder, 2009; Faner *et al.*, 2012; Yao and Rahman, 2012a; Yao and Rahman, 2012b; Kumar *et al.*, 2014). In the present review, we are not deliberating this topic. However, senescence in lung epithelial cells and fibroblasts is observed in both COPD and lung fibrosis, which raises the question of how senescence in both cell types leads to different pulmonary phenotypes? One of the mechanisms may be associated with the different senescence phenotypes (DNA damage-initiated senescence vs. MiDAS), leading to differential paracrine effects of SASP on neighbouring cells.

Mitochondrial dysfunction in chronic lung diseases

There is accumulating evidence showing that mitochondrial function is abnormal during the development of chronic lung diseases including COPD, pulmonary fibrosis and BPD (Mizumura *et al.*, 2014; Schumacker *et al.*, 2014; Ahmad *et al.*, 2015; Ito *et al.*, 2015) (Table 1). Although these chronic lung diseases share a lot of similar mitochondrial abnormalities, the mechanisms by which similar mitochondrial modifications result in different pulmonary phenotypes are unknown. This may be due to cell-specific damage of mitochondrial function [e.g. epithelial cells (type I and II), (myo) fibroblasts, endothelial cells and muscle cells] in response to different stimuli. Various approaches including *in vitro*, *in vivo* and *ex vivo* experiments are employed to determine the casual relationship between mitochondrial dysfunction and chronic lung diseases.

Mitochondrial dysfunction in COPD

COPD is characterized by a persistent airflow limitation and lung function decline, where cigarette smoke is the main etiological factor. The pathogenesis of COPD involves a variety of cellular processes, including oxidative stress, inflammatory responses and cellular senescence.

It has been shown that primary bronchial epithelial cells from COPD patients have swollen mitochondrial elongation and fragmentation, swelling and cristae depletion (Hoffmann *et al.*, 2013). Furthermore, chronic cigarette smoke exposure causes mitochondrial dysfunction in lung epithelial cells (Hoffmann *et al.*, 2013). This is in agreement with the findings that cigarette smoke hampers exercise-induced an increase in mitochondria density through a biogenesis response in the brain (Speck *et al.*, 2011). This may be due to the reduction in PGC1α, a master regulator of mitochondrial biogenesis in the cells of COPD patients compared with cells from non-smokers and smokers (Hoffmann *et al.*, 2013). Interestingly, acute cigarette smoke up-regulates the expression of genes involved in energy metabolism, ETC, and oxidative phosphorylation in mouse lungs (Agarwal *et al.*, 2012). Similarly, cytochrome c oxidase activity and mtDNA-related gene (12S rRNA) are increased in skeletal muscle in COPD patients, which are inversely associated with the degree of arterial hypoxaemia (Sauleda *et al.*, 1998). This may be the compensatory mechanisms and adaptive

Table 1

Changes in mitochondrial morphology and function in chronic lung diseases

Mitochondrial dysfunction	COPD	Pulmonary fibrosis	BPD*
Morphology	Fragmentation and elongation	Fragmented, enlarged and swollen mitochondria	Abnormal
Biogenesis	Reduction of PGC1α-dependent biogenesis	Reduced mtDNA copy number	Impaired biogenesis
mtROS	Increased	Increased	Increased
Oxidative phosphorylation	Damaged	Impaired complex I and IV activity	Decreased complex I and II function
Mitophagy	Impaired mitophagy	Impairment of PINK1-mediated mitophagy	—
mtDAMP	Increased release of mtDNA and ATP	Increased release of mtDNA	—

*All findings were obtained from a rodent BPD model of hyperoxia.

responses needed to maintain mitochondrial homeostasis. Mice deficient in the synthesis of cytochrome c oxidase are protected from cigarette smoke-induced pulmonary inflammation (Cloonan *et al.*, 2016). Mitochondrial genome sequencing will further reveal the changes in mitochondria-related genes and their roles in the development of COPD. In fact, whole genome analysis in rat COPD is ongoing (Jiang *et al.*, 2014).

Mitochondrial dysfunction in muscle cells may contribute to the loss of muscle strength, leading to a decline in physical function, which is a systemic manifestation in COPD patients. Indeed, reduced mitochondrial biogenesis, impaired oxidative phosphorylation and increased mtROS generation, along with a reduction in UCP3, are also observed in skeletal muscles and airway smooth muscle cells from COPD patients (Gosker *et al.*, 2003; Russell *et al.*, 2004; Gosker *et al.*, 2006; Meyer *et al.*, 2013; Puente-Maestu *et al.*, 2013; Wiegman *et al.*, 2015; Wiley *et al.*, 2016). However, mitochondrial ETC function (i.e. oxidative capacity) in the inspiratory muscles is enhanced in patients with COPD (Ribera *et al.*, 2003). A further causal relationship between mitochondrial function and muscle atrophy as well as the development of COPD should be established to reveal the role of mitochondria in this disease.

Mitophagy, one of the methods by which the quality of mitochondria is controlled, has been shown to be involved in the pathogenesis of COPD. We and others have shown that cigarette smoke impairs mitophagy, leading to incomplete degradation of damaged mitochondria (Ahmad *et al.*, 2015; Ito *et al.*, 2015). These damaged mitochondria may accumulate in the perinuclear region where generating excessive mtROS leads to nuclear DNA damage and subsequent cellular senescence. This is corroborated by the finding that restoration of mitophagy by the overexpression of Parkin reduces cigarette smoke-induced DNA damage and cellular senescence when used in combination with a mtROS scavenger (Ahmad *et al.*, 2015). Indeed, the levels of Parkin are reduced in lung tissues of COPD patients compared with those of non-smokers and smokers (Ahmad *et al.*, 2015; Ito *et al.*, 2015), which further confirms the impairment of mitophagy in COPD. It is interesting to note that severe stress derived from high concentrations of cigarette smoke induces necroptosis (i.e. necrosis and apoptosis), which is mediated by PINK1-induced mitophagy (Mizumura *et al.*, 2014). During the mitophagy, lipofuscin accumulates within the lysosomes, which reduces the efficiency of the endosomal/lysosomal pathway, thereby rendering mitophagy incomplete. Therefore, it is possible that during stress induced by high concentrations of cigarette smoke, mitophagy is incomplete due to lipofuscin accumulation, which causes the release of undegraded pro-apoptotic proteins such as cytochrome c from mitochondria, resulting in necroptosis.

Morphologically, mitochondrial fragmentation is observed in cigarette smoke-exposed lung epithelial cells and airway smooth muscle cells, as well as in lungs from COPD patients (Hara *et al.*, 2013; Hoffmann *et al.*, 2013, 2014). This is due to the increased expression of Drp1 and Mfn2. Interestingly, we have observed the mixed morphological changes of mitochondrial fragmentation and elongation in lung fibroblasts (Ahmad *et al.*, 2015). These discrepancies may be due to cell-specific responses to different concentrations and durations of cigarette smoke exposure.

mtDNA is considered to be a mitochondrial DAMP once it is released from mitochondria, thereby leading to inflammatory responses. As compared with that in non-smokers, mtDNA copy number in the circulation is increased in smokers and COPD patients (Pouwels *et al.*, 2014). Similarly, the mtDNA of cytochrome c oxidase-I and cytochrome c oxidase-II is increased in exfoliated cells in saliva from smokers as compared with non-smokers, and this increase positively correlates with number of years spent smoking and number of cigarettes smoked (Masayesva *et al.*, 2006). This is in agreement with the findings that cigarette smoke exposure causes mtDNA release from neutrophils, which may amplify airway inflammation (Heijink *et al.*, 2015). An increase in mtDNA release may be associated with cigarette smoking-induced impairment of mitophagy (Oka *et al.*, 2012, 2015) and the opening of a MPTP (Naserzadeh *et al.*, 2015); this needs to be investigated further. In addition to mtDNA, the opening of a MPTP causes cytochrome C release and ATP depletion, leading to apoptosis and inflammation.

Extracellular ATP acts as a DAMP and activates P2 nucleotide receptors, which are increased in bronchoalveolar lavage fluids of smokers and COPD patients as well as in mouse lungs with emphysema (Mortaz *et al.*, 2009; Lommatzsch *et al.*, 2010). Moreover, ATP neutralization or non-specific P2 receptor blockade significantly attenuates cigarette smoke-induced lung inflammation and emphysema (Cicko *et al.*, 2010). A recent study revealed the important role of $P2Y_{14}$ receptors in stress-induced stem cell senescence (Cho *et al.*, 2014), which raises the question of whether P2Y receptors modulate cigarette smoke-induced lung cellular senescence in COPD. These findings suggest potential therapeutic avenues using adenosine P2 receptor antagonists or inhibitors of ATP or the inflammasome for COPD.

In addition to tobacco smoking, other factors, such as hypoxia, hypercapnia, corticosteroid therapy, infection and a sedentary lifestyle, are all also able to cause mitochondrial dysfunction (Gayan-Ramirez and Decramer, 2013; Meyer *et al.*, 2013), despite their mechanisms being not fully understood. This may contribute to the pathogenesis and exacerbation of COPD as well as its co-morbidities such as skeletal muscle atrophy (Gifford *et al.*, 2015; Liu *et al.*, 2016). Overall, the targeting damaged mitochondria would be a promising strategy to attenuate the progression and exacerbation of COPD.

Mitochondrial dysfunction in pulmonary fibrosis

The main feature of pulmonary fibrosis is the excessive accumulation and deposit of extracellular matrix, thereby leading to the scar and loss of elasticity in lungs. Both fibroblasts and myofibroblasts are the principal effector cells of the lung for the generation of extracellular matrix (Yao and Li, 2015).

Recent studies have highlighted the importance of mitochondrial function and mitophagy in the pathogenesis of lung fibrosis (Bueno *et al.*, 2015; Patel *et al.*, 2015). It has been shown that damaged or dysfunctional mitochondria accumulate in alveolar epithelial cells of patients with idiopathic pulmonary fibrosis. mtDNA copy numbers are significantly

reduced in mouse lungs with bleomycin-induced fibrosis (Gazdhar *et al.*, 2014). The mtDNA encoded respiratory chain, such as cytochrome c oxidase subunit I, is reduced in mouse lungs with fibrosis and in lung epithelial cells treated with TGF-β (Sohn *et al.*, 2012; Gazdhar *et al.*, 2014). These findings suggest that both mitochondrial biogenesis and oxidative phosphorylation are reduced during lung fibrosis.

Further investigations have revealed that the accumulation of these dysfunctional mitochondria is due to the impairment of PINK1-mediated mitophagy, but not mitochondrial biogenesis (Bueno *et al.*, 2015). This is in contrast to the findings that vascular mitochondrial biogenesis is activated in response to asbestos and bleomycin inhalation (Carraway *et al.*, 2008). Furthermore, PINK1 deletion enhances bleomycin-induced pulmonary fibrosis in mice (Patel *et al.*, 2015). Hence, PINK1-mediated mitophagy is important for the maintainance of mitochondrial homeostasis (i.e. Ppargc1a, Tfam and cytochrome c) and dynamics in epithelial cells, thereby protecting against the development of lung fibrosis. Fibroblasts and myofibroblasts are the effector cells for the development of lung fibrosis. However, it is not clear whether mitochondrial dysfunction and mitophagy impairment occur in (myo)fibroblasts during pulmonary fibrosis. Also further studies are required to determine how mitochondrial dysfunction in lung epithelial cells interacts with (myo) fibroblasts, leading to fibrogenesis.

It has been shown that once released mtDNA recruits peripheral blood mononuclear cells and stimulates epithelial cells to generate TGF-β1 (Li *et al.*, 2015). Targeting mtDNA by DNase I protects against paraquat-induced pulmonary fibrosis (Li *et al.*, 2015). Interestingly, TGF-β1 increases the number of mitochondria, mitochondria-specific proteins, voltage-dependent anion channels, adenine nucleotide transporter and mtDNA content, whereas mitochondrial oxidative phosphorylation and mitophagy are impaired during fibroblast differentiation (Negmadjanov *et al.*, 2015; Sosulski *et al.*, 2015). We propose that mitochondrial biogenesis is needed for fibroblast differentiation that this effect is further promoted by mitophagy impairment and damaged mitochondria during fibrogenesis. However, it is not clear how TGF-β1 alters mitochondrial homeostasis, inducing the accumulation of damaged mitochondria and subsequent fibrogenesis.

Aging has been shown to participate in the pathogenesis of lung fibrosis as both mitochondria respiration and mitophagy are compromised in aging, whereas the levels of the mitochondrial biogenesis marker PGC1α, mitochondrial transcription factor A Tfam and mitochondrial gene cytochrome c are comparable between young and old mouse lungs (Bueno *et al.*, 2015; Sosulski *et al.*, 2015). Interestingly, there is no significant difference in the severity of fibrosis, in response to bleomycin, between young and aged mice, whereas fibrosis resolution is impaired in aged mice (Hecker *et al.*, 2014). This is ascribed to the accumulation of senescent myofibroblasts that are resistant to apoptosis in aged mice. Recent studies have shown that fibroblasts that resist cigarette smoke-induced cellular senescence acquire a pro-fibrotic phenotype (Kanaji *et al.*, 2014; Ahmad *et al.*, 2015), which may explain the fibrotic lesions occurring in COPD. Interestingly, primary lung fibroblasts derived from patients with idiopathic pulmonary fibrosis exhibited accelerated cellular senescence, where senescent fibroblasts express increased levels of the myofibroblast marker α-smooth muscle actin (α-SMA) (Yanai *et al.*, 2015). The mechanisms underlying these discrepancies in the causal relationships between fibroblast senescence and differentiation into myofibroblasts are not clear. Removing senescent fibroblasts would reveal whether senescence promotes their differentiation into myofibroblasts. In addition to (myo)fibroblasts, lung epithelial cells undergo senescence during the development of pulmonary fibrosis (Minagawa *et al.*, 2011; Shivshankar *et al.*, 2012). Further studies are required to determine their contributions to the pathogenesis of lung fibrosis and how these senescent cells interact with each other (autocrine and paracrine) to induce fibrogenesis.

Mitochondrial dysfunction in BPD

BPD is a chronic lung disorder of infants with low birth weight and in those who receive prolonged mechanical ventilation with oxygen to treat respiratory distress syndrome (McEvoy *et al.*, 2014). Antenatal and/or post-natal exposure to stress including mechanical ventilation, oxygen toxicity and pulmonary and systemic infection disrupts pulmonary development, thereby leading to inflammation and damage to the highly vulnerable premature lung in BPD. New BPD develops at the canalicular and early saccular phases, whereas old BPD starts at the saccular and alveolar phases of lung development. New BPD is pathologically characterized by the simplified alveolarization and vascularization, which is in contrast to severe lung injury with fibrosis in old BPD (Kramer, 2008).

Accumulating evidence shows that mitochondria are dysfunctional and respiration rates, ATP-production rate and complex I activity reduced in hyperoxia-exposed lungs in a mouse model of BPD (Ratner *et al.*, 2009). This is consistent with the reduced mitochondrial aconitase activity observed in lungs of baboons exposed to hyperoxia (Morton *et al.*, 1998). *In vitro*, hyperoxia decreases glycolytic capacity, glycolytic reserve and oxidative phosphorylation in mouse lung epithelial cells and inhibits complex I and II function, but not complex IV activity in mouse isolated lung mitochondria (Das, 2013). Furthermore, a complex I inhibitor delays alveolarization in neonate mice exposed to hyperoxia (Das, 2013). Impaired mitochondrial biogenesis may be responsible for hyperoxia-induced delayed alveolarization, which is the most common feature of BPD.

Hyperoxia-induced impairment of branching morphogenesis is associated with increased mtROS generation accompanied by increased mtDNA damage and mutation (Gebb *et al.*, 2013). Compared with nuclear DNA, mtDNA is prone to stress-induced damage and mutation due to lack of compact chromatin structure or DNA repair mechanisms. Indeed, the transmission of mtDNA mutations occurs in one in every 200 newborns, which potentially may cause disease or increase disease susceptibility (Elliott *et al.*, 2008). Treatment with a mitochondria-specific antioxidant, mitoTEMPO, during early post-natal hyperoxia protected against compromised alveolarization (Datta *et al.*, 2015), which suggests that targeted antioxidant therapy could be used to prevent or treat BPD. Hyperoxic exposure induces UCP2 expression in pulmonary macrophages and enhanced UCP3 levels in skeletal muscles in mice (Flandin *et al.*, 2005; Steer *et al.*, 2013), which may be compensatory responses to increased

oxidative stress and mtROS. Further studies are required to determine the role of UCP in the development of BPD using genetic manipulation approaches.

Recently, it has been shown that the NLRP3–PINK1 axis plays a pivotal role in hyperoxia-induced cell and tissue death in adult mice (Zhang *et al.*, 2014). Indeed, the NLRP3 inflammasome is critically involved in the development of BPD, as demonstrated using *in vivo* mouse and baboon models as well as *ex vivo* tracheal aspirates from BPD patients (Liao *et al.*, 2015). PINK1 deletion exaggerates hyperoxia-induced mtROS and apoptosis as well as lung injury (Zhang *et al.*, 2014). It is still not known whether PINK1-mediated mitophagy is impaired and how it is regulated during NLRP3-mediated inflammasome formation and subsequent BPD development. Additionally, there are no studies showing the changes in mitochondrial morphology and function in BPD patients; this needs to be investigated further.

A recent study has shown that 23 genes are differentially methylated with reciprocal changes in expression in patients with BPD compared with preterm or term lungs (Cuna *et al.*, 2015). Mitoepigenetics such as mitochondrial methylation occur in a variety of cultured mammalian cells, and this process is modulated by DNA methyltransferase 1 in mitochondria (Shock *et al.*, 2011, 2013, 2014). Therefore, it is possible that exposure to environmental factors including smoke, particulate metals and diet *in utero* leads to mtDNA methylation (Byun *et al.*, 2013), which renders newborns more susceptible to the development of BPD.

Conclusion and future directions

Mitochondria can function as a signal in addition to generating the energy needed for the survival of cells and their functions. Mitochondrial dysfunction plays an important role in the stress-induced inflammation and cellular senescence that occur in chronic lung diseases, such as COPD, pulmonary fibrosis and BPD. This is reflected by the findings that mitochondrial biogenesis, oxidative phosphorylation and mitophagy are reduced in chronic lung diseases.

A study using a rodent model has demonstrated that disruption of normal lung morphogenesis by lung-specific epithelial deletion of the CCAAT/enhancer-binding protein α in foetal life subsequently drives the onset of spontaneous pulmonary emphysema in adult mice (Didon *et al.*, 2010). This has leads to the hypothesis that the origins of COPD occur in early life. It is well known that mtDNA is inherited from the maternal side. Therefore, it would be interesting to study whether environmental stress causes dysfunctional mtDNA (e.g. mutation or epigenetic modifications) that are passed onto offspring, leading to the development of BPD and subsequently COPD. Employment of a mitochondrial–nuclear exchange technique will help to reveal the role of mtDNA in the pathogenesis of chronic lung diseases (Fetterman *et al.*, 2013; Betancourt *et al.*, 2014).

Mitochondrial transfer and replacement have recently been approved in the UK for use in the prevention and treatment of mitochondrial diseases (Mitalipov and Wolf, 2014; Dunham-Snary and Ballinger, 2015). It has been shown that mitochondrial transfer of induced pluripotent stem cell-derived mesenchymal stem cells to airway epithelial cells ameliorates cigarette smoke-induced airspace enlargement in mice (Li *et al.*, 2014). Similarly, mitochondrial transfer from stem cells protects against injurious and inflammatory responses in the lung evoked by LPS and allergens (Islam *et al.*, 2012, 2014). Tunneling nanotubes are considered as a duct to transfer healthy mitochondria to damaged cells, which are controlled by a mitochondrial Rho-GTPase (Miro1 encoding by Rhot 1 gene) (Ahmad *et al.*, 2014; Wang and Gerdes, 2015). However, it remains unclear how tunneling nanotubes are regulated particularly in the condition of lung injury. Further studies on mitochondrial dysfunction and transfer as well as their regulation would enhance the understanding of the molecular pathogenesis of chronic lung diseases and provide potential novel ways for treating them.

Author contributions

L.Y. and H.Y. drafted and edited the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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