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Mitochondrial Redox System, Dynamics, and Dysfunction in Lung Inflammaging and COPD

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Abstract

Myriad forms of endogenous and environmental stress will disrupt mitochondrial function by impacting critical processes in mitochondrial homeostasis such as mitochondrial redox system, oxidative phosphorylation, biogenesis, and mitophagy. External stressors that interfere with the steady state activity of mitochondrial functions are generally associated with an increase in reactive oxygen species, inflammatory response, and induction of cellular senescence (inflammaging) via mitochondrial damage associated molecular patterns (DAMPS) which are the key events in the pathogenesis of chronic obstructive pulmonary disease (COPD) and its exacerbations. In this review, we highlight the primary mitochondrial quality control mechanisms that are influenced by oxidative stress/redox system, including role of mitochondria during inflammation and cellular senescence, and how mitochondrial dysfunction contributes to the pathogenesis of COPD and its exacerbations via pathogenic stimuli.

Keywords

Oxidative phosphorylation; mitophagy; redox; telomere; DAMPs; inflammation; cellular senescence

1. Introduction

Although mitochondria are central in ATP generation, emerging evidence continues to highlight mitochondria's non-energetic roles in virtually all examples of eukaryotic biology. Innate immunity, apoptosis, and metabolism are largely regulated by mitochondrial mechanisms Mitochondrial quality control mechanisms, such as mitophagy and mitochondrial biogenesis are essential in cellular homeostasis. As organelles, mitochondria

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are sometimes observed as discrete units (blobs, circular, and tubular) and other times form high complexity networks distributed throughout the cytosol (Liu and Hajnoczky, 2011, Okamoto and Shaw, 2005).

In non-stressed healthy cells, mitochondrial ROS (mtROS) are scavenged by antioxidant proteins. However, they also serve as important molecules that engage in signal transduction and communicate cellular ATP energy status throughout multiple cellular pathways involving cytosolic calcium (Hamanaka and Chandel, 2010). In conditions of cell stress, disruption in calcium (Ca^{2+}) buffering within the matrix promotes apoptosis through release of cytochrome c which occurs in conjunction with changes in the capacity of mtROS. Alterations in mtROS by stress can affect mitochondrial quality control mechanisms in various tissues leading to activation of inflammatory pathways that may influence pathological processes (Minutoli et al., 2016, Park et al., 2013). In this review, we discuss the primary mitochondrial quality control mechanisms that are influenced by oxidative stress, examine how mitochondria play a role in cell inflammation, and cite how mitochondrial dysfunction plays a central role in chronic airways disease, such as in the pathogenesis of chronic obstructive pulmonary disease (COPD), a disease of inflammaging.

1.1. *Mitochondria and reactive oxygen species (ROS)*

The role of ROS in cells and disease has been an extensively studied as well as hotly debated within the last decade. A number of animal models reveal that targeted mitochondrial dysfunction (at times accompanied by elevated mtROS) is associated with positive effects on organismal health and lifespan. This suggests that mtROS are not de facto toxic by-products of respiration, a paradigm in biology previously held in greater consensus. The thresholds and timing of ROS stress regarding hermetic means of organismal protection lacks clarity (De Haes et al., 2014, Ristow and Schmeisser, 2014). Thus, we are only beginning to understand how mtROS functions as an integral component in normal cell physiology. For instance, in lung endothelial cells cultured under low oxygen tension (hypoxia), suppressing perinuclear localization of mitochondria, impedes mtROS-mediated VEGF transcription (Al-Mehdi et al., 2012). Normally, hypoxia signals mitochondria to localize to the nucleus resulting in ROS mediated upregulation of VEGF. The VEGF gene under hypoxia is specifically directed by nucleosome dynamics to expose its locus to ROS resulting in its transcriptional activation (Grishko et al., 2001, Ruchko et al., 2009). Other mechanisms of mtROS dynamics involve mitochondrial quality control mechanisms that appear to be critical for mediating physiological responses to stress. It can be observed that microglial cells deficient in mitochondrial fission are protected from LPS mediated ROS production associated with inflammatory pathway activation (Park, Choi, 2013). Such discoveries highlight the importance of mtROS as a regulator of tissue physiology. In this regard, the regulation of mtROS in healthy tissue appears to serve important roles for cell homeostasis versus mtROS produced when associated with stress and disease (Hamanaka and Chandel, 2010, Shadel and Horvath, 2015). Therefore, targeting mtROS therapeutically will likely require careful considerations of treatment duration/dose and disease context.

1.2. ROS versus Reactive Sulfide Species (RSS) in mitochondria

Although each of the electron transport chain (ETC) complexes have now been shown produce superoxide ($O_2^{\cdot -}$), the primary sites where electron leak occurs are complex I (NADH dehydrogenase) and complex III ($CoQH_2$-cytochrome *c* reductase) which releases superoxide into both the inner membrane space and the matrix (Muller et al., 2004, Turrens, 2003). Hydrogen peroxide (H_2O_2) is thought to be an ideal ROS transducer for relaying mitochondrial status and metabolism signals. H_2O_2 also undergoes relatively slower enzyme mediated kinetics when reacting with thiol groups on redox sensitive target proteins (Forman et al., 2010). In contrast, $O_2^{\cdot -}$ that is not dismutated can react with available nitric oxide to form peroxynitrite ($ONOO^-$). Diffusion of $ONOO^-$ occurs rapidly and inhibits enzyme activity within mitochondria and cytosol in addition to nitrosating nuclear DNA (Ballinger et al., 2000, Brown and Borutaite, 2004).

DeLeon et al. study recently brought into question whether ROS molecules should be presupposed as the bonafide signal transducing molecules since they were unable to easily distinguish between ROS and reactive sulfide species (RSS) using a host of indicative ROS sensitive probes that have been used in countless studies (DeLeon et al., 2016). Sulfur metabolites may be a therapeutic target in suppressing inflammation in acute lung injury (Sakaguchi et al., 2014). However, the interplay between ROS and RSS mediated chemistry in mitochondria is poorly understood. Unlike ROS, RSS may also function in cell signaling, thereby influence inflammatory pathways. Although RSS mediated protein modifications have been identified and are proposed to produce poly-sulfide chains on cysteine residues, the modulatory function remains unclear (Mishanina et al., 2015). Future work and new selective biochemical tools will be necessary to delineate independent roles of ROS versus RSS in contributing to mitochondrial signaling networks and how they are involved in physiological changes.

2. Mitochondrial Stress Response

2.1 *Mitophagy mechanisms*

Mitochondria are sensitive to loss of membrane potential ($\Delta\Psi m$). Inability to maintain basal $\Delta\Psi m$ is considered as a state of mitochondrial stress which can result from exposure to certain toxic chemicals, environmental agents (e.g. cigarette smoke, bacterial and viral infection), nutrition and age (Kovacic et al., 2005, Meyer et al., 2013b). To retain functionality throughout its compartment, mitochondria utilize mitophagy as a protective mechanism by minimizing the fraction of dysfunctional mitochondria and sustaining an adequate supply of healthy mitochondria with intact $\Delta\Psi m$. How this process might be globally regulated? The process of mitochondrial fission and fusion has been discovered to play a major role in selecting mitochondria for mitophagic turnover. This early step in mitophagy is first accomplished through asymmetrical fission (**Figure 1**). Once stressed, severely damaged/depolarized mitochondria are segregated from the functional pool and blocked from achieving inner-membrane fusion with functional mitochondria (Baker et al., 2014, Twig et al., 2008). Mitochondrial surface proteins Mitofusin 1 and 2 (Mfn1 and Mfn2) together with optic atrophy 1 (OPA1) modulate the fusion process (Anand et al., 2014, Song et al., 2007). A recent study reports the central role of PINK-Mfn2-Parkin-mediated

mitophagy during perinatal metabolic transformation (switching from glycolytic to fatty acid metabolism) in mouse heart. MFN2 mutant lacking PINK1 phosphorylation sites necessary for Parkin binding (Mfn2 AA) inhibited mitochondrial Parkin translocation, thereby suppressing mitophagy without affecting mitochondrial fusion. Cardiomyocyte-specific Parkin ablation early after birth, before 3 weeks of age in mice was lethal since it prevents postnatal mitochondrial maturation that is required for it survival. Thus this study shows novel role of Parkin during perinatal mitochondrial maturation in cardiomyocytes (Gong et al., 2015). The prominent effector of mitochondrial fission is dynamin 1-like (Drp1) which is regulated through its recruitment from the cytosol to mitochondrial outer membrane by multiple receptors (Loson et al., 2013). Recently, the cellular energy sensor AMPK has been shown to be central in modulating mitochondrial fission and fusion dynamics in response to disruption in ΔΨm by activating mitochondrial fission factor (MFF) (**Figure 1**). MFF then acts to promote Drp 1 mediated fission events (Toyama et al., 2016). However, it is not yet well understood if dysfunctional constituents of mitochondria are segregated from functional components in fission. It is thought they may be partitioned prior to fission to isolate regions of mitochondrial from the network (Youle and van der Bliek, 2012). Healthy mitochondria or mitochondrial species able to be rejuvenated can continuously re-enter into the mitochondrial network for energy production and cell signaling.

The mechanisms to scout for dysfunctional mitochondrial species within the cytosol, involve stabilization of PTEN-induced putative kinase 1 (Pink1) on the outer membrane following loss of ΔΨm (Matsuda et al., 2010). The E3 ligase Parkin is recruited to catalyze K63-linked ubiquitination of outer membrane proteins. Though this event is dispensable for mitophagy, (Narendra et al., 2010) it facilitates targeting of mitochondria to form autophagosomes (Hattori et al., 2014). Recent insight into the mitophagy mechanism highlights a major role for Pink1 in phosphorylation of ubiquitin residues which contributes to Parkin activation (Koyano et al., 2014). The activity of Parkin meditated mitophagy following loss of ΔΨm also requires mitochondrial-autophagosome targeting receptor Nix/Bnipl (Ding et al., 2010). Parkin is additionally coordinated to potentiate proteolytic degradation of Mfn1/2 on the OM of depolarized mitochondria to suppress fusion. However, Parkin has also been observed to coordinate events that weigh heavily towards suppression of fission by targeting Drp1 for proteasomal degradation (Wang et al., 2011). Drp1 degradation is also associated with mitochondrial elongation. This may occur under stress conditions where Parkin is not involved in promoting mitophagy (**Figure 3**). Mitophagy receptor FUN-14 domain containing protein 1 (FUNDC1) role in mitochondrial dynamics and mitophagy was recently reported using HeLa cells. FUNDC1 interacts with both DRP1 and OPA1 to regulate mitochondrial fission or fusion and mitophagy. They have also showed that OPA1 interacts with FUNDC1 via its Lys70 residue and mutation of K70 to Ala (A) but not Arg (R) abolished the interaction suggesting FUNDC1 role in the regulation of mitochondrial dynamics and quality control (Chen et al., 2016). Hypoxia appears to be an inducer of FUNDC1 mediated fission by mediating loss of its interaction with ER protein CANX (Wu et al., 2016).

Recent studies have provided evidence that AMBRA1-ActA, Smurf1, and Gp78 are involved in Parkin independent mitophagy processes. The bacterial autophagy receptor

NDP52 mediates clearance of mitochondria in Parkin negative cells (Lazarou et al., 2015). Smurf1 like Parkin, is an E3 ligase and is essential for damaged mitochondria to be targeted to autophagosomes (**Figure 1)**. Interestingly, Drp1 is essential for Parkin independent mitophagy (Kageyama et al., 2014). Mitochondrial depolarization by protonophore carbonyl cyanide *m*-chlorophenylhydrazone (CCCP) allows Pink1 and Drp1 to associate and together, they promote Parkin mediated mitophagy (Buhlman et al., 2014). Role of Parkin in the fission/fusion aspect of mitphagy depends on combinatorial phosphorylation events of specific Drp1 residues by either calcium/calmodulin-dependent pk-Iα to promote fission or Protein Kinase A (PKA) to inhibit fission (Buhlman, Damiano, 2014, Chang and Blackstone, 2007). Parkin's redundancy in the mitophagy process, its dispensability, and conflicting reports in its role in the fission/fusion process raises the possibility that Parkin functions as a "tuner" for various mechanisms in mitophagic dynamics. In its mobilization for mitophagy, it could either promote fusion to temper down mitophagy or enhance fission together with its role in ubiquitinating mitochondrial proteins for mitochondria to autophagosome targeting. Thus, the damaged mitochondria are removed by mitochondria quality control (mitophagy) which may thus remove excess mtROS, mtDNA, and other associated factors. Recently reported *in vivo* mitophagy model a transgenic mouse expressing mitochondrial-targeted form of the fluorescent reporter Keima (mt-Keima) can be efficiently exploited in understanding the process of mitophagy occurring *in vivo* under different environmental stressors (Sun et al., 2015). Future studies will use this valuable resource that includes both primary cells and tissues from mt-Keima mice to understand chronic lung diseases where mitophagy plays an important role.

2.2. *Mitophagy in COPD*

While the underlying mechanisms that promote chronic obstructive pulmonary disease (COPD) progression are not yet clear, recent studies identify changes in lung cell mitochondria that might contribute to its pathogenesis. Inflammaging is central features in the pathogenesis of COPD. The persistence in airflow constriction and parenchymal damage in COPD follows unresolved inflammatory processes and signals from both parenchymal cells and infiltrate. Tissue remodeling ensues, and acute exacerbations due to pollutants, allergens, or infection heighten the inflammatory response. Bronchial epithelial cells from COPD patients exhibit swollen, elongated mitochondria in addition to fragmentation and disruption of cristae (Hoffmann et al., 2013). Although 20% of COPD cases include non-smokers, most COPD patients have a prior history of cigarette use which is reflected by signs of mitochondrial dysfunction in smoke exposed lung epithelial cells (Hoffmann, Zarrintan, 2013, Lamprecht et al., 2011). In Beas-2B lung cells treated with cigarette smoke (CS) extract, the changes in mitochondrial structure persisted for at least 3 months following 3 months of CS extract treatments (Hoffmann, Zarrintan, 2013). Similarly, tobacco smoke impairs ETC complex function in the brain and reflecting mitochondrial dysfunction systemically (Speck et al., 2011). This is also observed in muscle cells in COPD subjects where mitochondrial dysfunction may contribute to loss of strength as a systemic manifestation of COPD. This may be due to impaired oxidative phosphorylation and increased mtROS in skeletal muscles and airway smooth muscle cells (Meyer et al., 2013a, Puente-Maestu et al., 2013, Wiegman et al., 2015). The airway hyperresponsiveness in mice exposed to oxidative stress through ozone exposure in addition to levels of TGF-β and IL-8

in the ASM cells from COPD patients were attenuated by MitoQ mitochondrial antioxidant (Wiegman, Michaeloudes, 2015). Asthma-COPD overlap syndrome (ACOS) includes features of both complications though is difficult to medically define. A study measuring blood level of mtDNA in ACOS patients revealed an increase in the ratio of mtDNA to nuclear DNA. Mitochondrial dysfunction is reflected in the mtDNA increase found in blood cells due to the inflammatory characteristics of the disease (Carpagnano et al., 2016). The combination of symptoms between asthma and COPD may allow for a more distinctive diagnosis for ACOS while underscoring a role for mitochondrial dysfunction in its etiology. However, not much information is known about physiopathological changes in in ACOS based on mitochondrial dysfunction. It is possible that the release of mtDNA and damage associated molecular patterns (DAMPS) occur in ACOS and during its exacerbations. Of a panel of lung metabolites analyzed in a model of progressive mouse emphysema, levels of L-carnitine were most significantly reduced (Conlon et al., 2016). Carnitine being essential to long chain fatty acid transfer into mitochondria may contribute to mitochondrial dysfunction. There is a litany of diseases involving disruption to fatty-acid metabolism including metabolic cardiomyopathy in which carnitine transporter is impaired. Emerging evidence of mitochondrial dysfunction in other characterized diseases of fatty acid oxidation disorders involves changes in carnitine dynamics (Sharma and Black, 2009, Wajner and Amaral, 2016). Iron-responsive element-binding protein 2 (IRP2) has been identified as a leading candidate for COPD susceptibility gene in humans based on genome-wide association studies (DeMeo et al., 2009). Recently, using an Irp2 deficient mouse, the role of Irp2 as a regulator of mitochondrial function has been demonstrated. Irp2 KO mice were protected from CS-induced COPD. Irp2 increases mitochondrial iron loading and levels of cytochrome *c* oxidase (COX), which led to mitochondrial dysfunction and successively COPD. Mice treated with mitochondrial iron chelator or low iron diet were protected from CS-induced impairment of mucociliary clearance, inflammation, and lung injury during experimental COPD suggesting functional role of mitochondrial-iron axis as potential therapeutic target for COPD (Cloonan et al., 2016). This alludes again to a central role for mitochondrial stress in progression of inflammatory state of chronic lung disease through changes in ability of mitochondria to manage fatty-acid metabolism and iron chelation. It remains to be seen whether iron chelation would have any repercussions on attenuation of dysfunctional mitophagy and cellular senescence in COPD.

Mitochondrial elongation induced by either Drp1 (dynamin-1-related protein that regulates mitochondrial fission) inhibition and/or Mfn2 overexpression is regulated by coordinated action of Pink1 and Parkin during mitophagy. Mitochondrial elongation has been shown to prevent mitochondria from mitophagic degradation (Gomes et al., 2011). We have shown that CS extract mediated stress increases mitochondria elongation and mtROS, and reduced ATP levels in lung epithelial cells and fibroblasts (Ahmad et al., 2015). The loss of mitochondrial $\Delta\Psi m$ is suspected to contribute to the inflammation associated with COPD in airway epithelial cells (Heijink et al., 2015). Furthermore, increased mitochondria mass is observed along with decreased Parkin mitochondrial translocation by CS extract which may explain the increase in mitochondrial mass being due to inhibition of mitophagy. These *in vitro* results are in agreement with studies reporting levels of Parkin are reduced in lung tissues of COPD patients and smokers **(Figure 4)** (Ahmad, Sundar, 2015, Ito et al., 2015).

Alternatively higher doses of CS extract treatment in immortalized Beas2B cells undergo mitophagy-dependent necropotosis mediated by PINK1-induced mitophagy (Mizumura et al., 2014). Other studies report the accumulation of damaged or dysfunctional mitochondria due to impaired mitophagy in chronic diseases including COPD (Hoffmann, Zarrintan, 2013, Ito, Araya, 2015, Meyer, Zoll, 2013a). This suggests that mitochondrial structural changes and/or its dysfunction by CS extract lead to impaired mitophagy. However the molecular mechanism of these phenomena (i.e. impaired mitophagy-telosome signaling) in the pathogenesis of chronic lung diseases is not known.

3. Mitophagy and senescence: implications for COPD pathogenesis

Defective mitophagy or dysfunctional mitochondrial metabolism is linked with aging and aging-related disorders (Bueno et al., 2015, Palikaras and Tavernarakis, 2012, Patel et al., 2015). Pink1 and Parkin knockout (KO) mice exhibit increased ROS levels and dysfunctional mitochondria suggesting that these proteins may be critical for preventing senescence (Gispert et al., 2009, Palacino et al., 2004). Parkin or Pink1 knockdown enhances mtROS production by (cigarette smoke extract) CS extract which is concurrent with increase in cellular senescence (Ito, Araya, 2015). Parkin overexpression has been shown to increase the lifespan in flies, partly due to reduced oxidative stress by activating mitophagy (Rana et al., 2013). However, there is no information available regarding the role of Pink1/Parkin-mediated mitophagy in cigarette smoke-induced lung injurious responses *in vivo*. We found that levels of Pink1 and Mfn2 were increased, but the levels of Parkin remain unaffected due to CS extract treatment in human lung fibroblasts and found that instead, Pink1 and Parkin colocalization was impaired which negatively affected mitophagy leading to increase in cellular senescence (Ahmad, Sundar, 2015). Hoshino et al. showed p53 binds to Parkin and restricts its translocation to mitochondria which compromises autophagy and promotes mitochondrial dysfunction (Hoshino et al., 2013). A recent study shows mtROS-dependent autophagy by CS extract regulates mucin expression (MUC5AC) through the c-Jun N-terminal kinase (JNK) and activator protein-1 (AP-1) signaling pathway in human bronchial epithelial cells thereby re-emphasizing how autophagy inhibition can be targeted for treating chronic lung diseases (Zhou et al., 2016). Another report demonstrates role of mitochondrial E3 ubiquitin protein ligase 1 (MUL1) in CS-induced pulmonary endothelial cell death and dysfunction via Akt ubiquitination/degradation (Kim et al., 2016). As a factor that plays a critical role in mediating both apoptosis and senescence, this work suggests p53 mechanism for inducing senescence may occur through Parkin inhibition allowing dysfunctional mitochondrial to persist. Parkin expression also is transactivated by p53 so it is possible there are additional levels of regulation regarding p53 mediated activity on Parkin (Zhang et al., 2011). Further investigation is necessary to shed light on Parkin/Pink1 role in in p53 and p16-dependent cellular senescence.

3.1. *Mitochondrial elongation in senescence*

Based on the prior reports the role of mitochondrial elongation implies to play an integral part during cellular senescence process which remains unclear. The MARCH5 mitochondrial E3 ligase binds to Fis1, Drp1, and Mfn2. Either a mutant or knockdown of MARCH5 suppresses Drp1 mediated fission and results in mitochondrial elongation and significant

increase in SA-β-gal activity reflecting senescence (Park et al., 2010). Mitochondrial fusion in response to cell stressors including inhibition of translation and UV irradiation requires mitochondrial scaffolding protein SLP-2 to support Opa1 fusion activity (Tondera et al., 2009) (**Figure 3**). Though senescence was not a parameter of the Tondera et al. study, the "stressors" utilized to achieve mitochondrial elongation have been used previously as modes of senescence induction (Chainiaux et al., 2002, Robles and Adami, 1998, Tavana et al., 2010). Therefore, understanding the role of SLP-2 in the establishment of senescence would contribute to the role of mitochondrial elongation in senescence. Especially because depleting both Fis1 (fission) and OPA1 (fusion), resulted in greater mitochondrial fragmentation which protected against senescence. Depletion of Fis1 alone promoted senescence (Lee et al., 2007). This could suggest mitochondrial elongation is a key process in transitioning into senescence state since it has been shown that mitochondrial elongation is associated with resistance to oxidative stress once senescence is established (Mai et al., 2010). Others have hinted at this possibility by overexpressing Fis1 and showing that the inability for mitochondria to elongate after toxic stress protected from senescence (Yoon et al., 2006). Mitochondrial elongation due to inhibition of fission correlates with cell cycle arrest and senescence, and occurs in concert with decreased $\Delta\Psi m$, elevated mtROS, and DNA damage response (**Figure 3 and Figure 4**). Thus, there are aspects of the dynamic state in which mitochondria are regulated that controls senescence. This report (Lee, Jeong, 2007) is in line with our results showing CS extract causes mitochondrial elongation in fibroblast prior to undergoing stress induced-senescence (**Figure 3 and Figure 4**) (Ahmad, Sundar, 2015). However, specific cell types, dose and duration of CS extract treatment appear to be an important factor as how mitochondria respond to CS extract. Such is the case in airway smooth muscle cells which exhibit fragmentation (Aravamudan et al., 2014)) and alveolar epithelial cells in which CS extract produces both fragmentation and elongation depending on level of CS extract stress (Ballweg et al., 2014, Hoffmann, Zarrintan, 2013). These mixed observation in morphological changes (mitochondrial fragmentation and elongation) seen in different reports reveals variability in cellular response to CS extract which likely accounts for some of the differences in the outcome.

3.1. Mitochondrial elongation: Role of AMPK and NAD

Mitochondrial elongation is proposed to be an important survival mechanism (**Figure 3**). Starvation by nutrient depravation results in mitochondrial elongation and requires phosphorylation of Drp1 by PKA in early stages of mitochondrial dysfunction as cellular AMP rises (Gomes, Di Benedetto, 2011). Mitochondrial dysfunction in many cases is associated with a decrease in ATP which is also the typical metabolic state of senescent fibroblast (Zwerschke et al., 2003) and another report suggest that senecence can be triggered when ATP is depleted (Stockl et al., 2006). Clues to the mechanisms involved in triggering senescence through depletion of ATP might involve energy sensor AMPK on two regulatory fronts as the AMP:ATP ratio increases: 1) The ability of AMPK to directly upregulate p53 and p16 to establish cell cycle arrest (except in the context of H_2O_2 induced senescence where AMPK activation protects from senescence (Ido et al., 2012)) and, 2) The ability of AMPK to directly up-regulate mitochondrial fission factor (MFF), a receptor for Drp1 which is mobilized to induce mitochondrial fission for mitophagy during loss of mitochondrial $\Delta\Psi m$ (Toyama, Herzig, 2016). AMPK activate Sirt1 (which is decreased in

COPD associated with cellular senescence) can suppress senescence by increasing mitochondrial NAD^+ levels. However, in conditions of mitochondrial stress, if complex I is impaired in its ability to efficiently oxidize NADH (Forkink et al., 2015, He et al., 2013) and this represses Sirt1 activity (low NAD^+/NADH ratio), reduced AMPK could promote senescence instead. This may occur because disruption Sirt1-AMPK positive feedback might reduce AMPK ability to induce fission through MFF activation. It has also been reported that Sirt1 expression is absolutely required for AMPK activation (Price et al., 2012). Therefore, down regulation of Sirt1 could be a stressful event that promotes elongation through AMPK disruption. In this scenario, attenuated AMPK is less potent in its role in promoting mitochondrial fission through up-regulation of MFF (Toyama, Herzig, 2016). Furthermore, PKA not only promotes starvation induced mitochondrial fusion and elongation through inhibitory phosphorylation on Drp-1, but has also been shown to inhibit AMPK. To survive in the face of mitochondrial stress, elongation eventually promotes ATP production (Gomes, Di Benedetto, 2011). ATP mediated inhibition of AMPK might reinforce fission repression when integrated with increased PKA activity (**Figure 3**). These complex networks involving both energetic and non-energetic roles of mitochondrial function in connecting mitochondrial stress, elongation, and cellular senescence will require further study.

4. Cross-talk among mitochondria, telomeres, and shelterin (telosome) complex

Perinuclear mitochondrial accumulation is a critical step during mitophagy (Vives-Bauza et al., 2010) and perinuclear mitochondria clustering transmits nuclear signals via mtROS (Al-Mehdi, Pastukh, 2012) In continuance of this paradigm, oxidative and genotoxic stress are well known initiators of telomere dysfunction (Opresko et al., 2005). The mtROS specific scavenger mitoquinone (MitoQ) prevents telomere shortening and delays senescence (Saretzki et al., 2003). Also, it has been recently shown that telomere compromised mouse tissues sustain impaired mitochondrial function (Sahin et al., 2011). This occurs in a p53 dependent manner linking mitochondrial dynamics to telomere health. Telomeres have specialized nucleoprotein structures that protect or “cap” the linear ends of eukaryotic chromosomes from DNA repair, preventing aberrant repair and end-to-end chromosome fusions. Telomeres constitute TTAGGG DNA tandem repeats that are bound to a multiprotein complex called shelterin/telosome that contains six important proteins TRF1, TRF2, POT1 (POT1a and POT1b in mouse), TPP1, TIN2 and RAP1. Telomere loop formation by TRF2 protects its ends from recognition by DNA damage pathways (Doksani et al., 2013). A positive correlation is shown between telomere length and aging. However, in patients with COPD, telomere length of alveolar cells may not exhibit relative “shortening” while telomere damage persists and contributes to an aged phenotype (Birch et al., 2015). Telomere shortening is associated with aging, and current studies suggest an important role of telomere structure/organization, telomeric DNA damage, and telomere end capping proteins in various age-associated disorders (Armanios, 2013, Cheung et al., 2014). Accumulating evidence suggests a link between mitochondrial dysfunction and telomere attrition. Since p53 activity has been identified as a link between both the telomeric and mitochondrial compartments, it stands to reason other factors are likely to be involved as

well. This is corroborated by a recent study showing that TIN2 is localized to mitochondria apart from its nuclear compartment, which regulates metabolism and mtROS generation (Chen et al., 2012, Sullivan et al., 2012). Recently, telomere dysfunction and senescence-associated pathways were also identified in bronchiectasis patients. Larger airway epithelial cells from patients with bronchiectasis show increased γH2A.X and telomere-associated foci (telomeric DNA damage), increased p21 along with decreased Sirt1 expression (Birch et al., 2016). Telomerase, an enzyme that adds DNA sequence repeats to telomere, can also translocate into mitochondria regulating mitochondrial function and mtROS-mediated DNA damage (Ahmed et al., 2008, Santos et al., 2004, Santos et al., 2006, Singhapol et al., 2013).

5. Defective mitochondrial biogenesis in COPD

One possibility for cigarette smoke mediated mitochondrial dysfunction is impaired mitochondrial biogenesis. PGC1α, involved in mitochondrial biogenesis is reduced in the lung in moderate to severe COPD patient's vs non-COPD patients. Interestingly, mild severity COPD exhibited elevated levels of PGC1α beyond both COPD and non-COPD subjects raising the possibility that PGC1α is an important factor in limiting the progression of COPD towards more severe stages (Li et al., 2010). Previous report suggests that mouse exposed to 4 weeks of CS led to up-regulation of mRNA involved in energy metabolism and oxidative phosphorylation in mouse lung. This may be a response to limited pyruvate after CS exposure since glucose metabolism appears to be concordantly rerouted into the pentose phosphate pathway (PPP) (Agarwal et al., 2012). Notably, a bolstered PPP pathway has been implicated in tumorigenesis and metastasis as well in studies (Patra and Hay, 2014). In skeletal muscle biopsy from COPD patients, authors noted a futile up-regulation in mitochondrial biogenesis DNA replication factor Tfam in muscle fibers that were oxidatively deficient. Since the fibers were also accompanied by increased mtDNA oxidation and deletions, Tfam up-regulation appeared to do nothing to protect against loss of oxidative functions. Similar to CS exposed mouse lung, a number of transcripts related to metabolism were upregulated in the COPD skeletal muscle (Konokhova et al., 2016).

6. Mitochondrial-derived vesicles

Mitochondrial quality control also appears to incorporate important mitophagy independent processes involving mitochondria-derived vesicles (MDVs). MDVs can be formed in response to mitochondrial stress and do not require diminution of mitochondrial membrane potential. These MDVs serve to enrich oxidized proteins and lipids and ultimately deliver them to lysosomes for degradation (**Figure 2**). Interestingly, normal MDVs contain specific cargo including OxPhos, but the stress induced MDVs do not contain nucleoids and enrich proteins from ETC complexes II, III, and IV while I and V are excluded, (Neuspiel et al., 2008, Soubannier et al., 2012a, Soubannier et al., 2012b). Mitochondria-derived vesicles (MDVs) can be formed during mitochondrial quality control (Sugiura et al., 2014). MDVs contain mitochondrial energetics, such as OxPhos (Panfoli et al., 2016). Recent work also suggests MDVs are induced by Pink1 and Parkin activity in response to mitochondrial oxidative stress (**Figure 2**). This appears to occur prior to mitophagy (first 2 hours of mtROS stress) and is thus an early event in the mitochondrial stress response (McLelland et al., 2014).

Distinguished from MDVs are less well understood mitochondrial spheroids which have also been shown to be a quality control process. Like autophagy spheroids form sequestration membranes that engulf other mitochondria, endoplasmic reticulum, and incorporate lysosomal proteins. In liver, these spheroids are inducible by acetaminophen overdose which leads to severe mitochondrial oxidative stress. Interestingly, mitochondrial spheroid production due to $\Delta\Psi m$ depolarization appears to be a Parkin dependent process involving mitofusin (Mfn1/2) degradation (Ding et al., 2012, Yin and Ding, 2013). However, Parkin, in contrast to its promotional activity in mitophagy induction or MDV formation, suppresses mitochondrial spheroid formation via Mfn1/2 degradation. Thus, mitophagy and MDV are preferred routes for responding to mitochondrial stress and spheroid formation occurs as a "last ditch effort" to maintain homeostasis in conditions of severe damage to the cell. Spheroids may be critical to regaining cell viability and organismal recovery by acute toxicity. Further studies are required to understand the regulation, interaction, and cross-talk between spheroid induction and mitophagy following mitochondrial stress.

7. Mitochondrial dysfunction and DAMP signaling in inflammation

Stress induced mtROS increase triggers the activation of inflammasome pathway. The multi-oligomer inflammasome is an innate immune modulator. Both infectious molecules and endogenous molecules originating from sites of injury or disease related abnormalities activate inflammasome through NF-κB pathway. Pro-IL1β and pro-IL-18 are processed by the inflammasome NLR family pyrin domain (NLRP3) following activation of caspase-1 to produce the mature pro-inflammatory mediators. Pharmacological inhibitors of Complex I or III raise mtROS and subsequently activate the inflammasome (Zhou et al., 2011) and mitochondrial antioxidant MitoQ may restore mitochondrial function. The exact mechanisms as to how mitochondrial stress elicits inflammatory signaling are still murky. Inflammasome independent pathways are activated following the induction of metabolic stress through fatty-acid induced ETC uncoupling (Freigang et al., 2013). This alludes to the existence of other mechanisms for inducing inflammation following altered mitochondrial function that do not necessarily involve pathogens or oxidative stress (Ren et al., 2016). In macrophages mitophagy protects against inflammation which can limit tissue repair by reducing damaged mitochondrial signaling from the Nlrp3- inflammasome (Zhong et al., 2016). Mitochondrial redox changes that release ROS as damage signals may also be accompanied by the release of mtDNA and ATP into cytosol or circulation leading to further mitochondrial dysfunction (Tamura et al., 2011, Yu et al., 2014). The mtDNA and ATP released from damaged mitochondria are considered mitochondrial damage associated molecular patterns (DAMP). Mitochondrial ATP may be released through pores or are regulated by vesicular and active transport, which are seen in neurons, fibroblasts, epithelial cells, neutrophils, and macrophages (Fitz, 2007). In the case of damaged membranes ATP easily diffuses **(Figure 2)**. The activation of cell surface purinergic receptors P2 receptors results in increased mtROS, and pro-inflammatory mediators including the Nlrp-inflammasome which is stimulated by extracellular ATP.

Release of mtDNA by distressed mitochondria can bind directly to the Nlrp component of the inflammasome (**Figure 2**). Furthermore, Nlrp3 activation is purported to require interaction directly with cardiolipin, a membrane lipid exclusive to the mitochondrial IM

(Iyer et al., 2013). The absent in melanoma 2 flavor of inflammasome (distinct from Nlrp inflammasome) instead, exhibits higher affinity for the non-oxidized mtDNA (Shimada et al., 2012). The propensity for oxidized mtDNA to bind Nlrp compared to non-oxidized mDNA reveals a possible mode of regulation. Additionally, a role for DNase II has been shown in protecting against tissue inflammation by digesting mtDNA (**Figure 2**). RNAi mediated knockdown of DNase II leads to the induction of autophagy and enhanced TLR9 signaling suggesting that can down regulate the inflammasome response despite increased mtDNA damage (Ding et al., 2013). Cell surfaces receptors of the Toll-like, in particular TLR9, are involved in the activation of mtDNA mediated Nlrp-inflammasome response for mitochondria that have escaped mitophagy (Oka et al., 2012). RNA virus is able to induce Nlrp-inflammasome activation through initiating formation of the programed necrosis Rip1-Rip3 complex and driving mitochondrial dysfunction. Nlrp activation is followed by recruiting Drp1 to mitochondria and supporting fragmentation (Wang et al., 2014).

mtDNA release occurs through opening of the mitochondrial permeability transition pore (MPTP) and formation of exosomes harboring mtDNA (e.g. MDVs) that are secreted extracellularly. Inflammatory signaling can stimulate opening of MPTP. The release of mtDNA is prevented by MPTP inhibitor cyclosporine A (Gao et al., 2013). Following injury, infection, or age-related changes, TNFα mediated activation of NF-κB and opening of MPTP, would facilitate mtDNA release and further stimulate NF-κB through TLR9 in an autocrine or paracrine fashion to support inflammasome activation. Here, inflammatory response and secretion of mtDNA converge to amplify the damage signal (**Figure 2**). In chronic inflammation associated with mitochondrial dysfunction inhibition of MPTP or deactivating mtDNA exosomes might be an avenue for tempering disease progression which is not been tested yet. Lack of inflammatory resolution suggests the tissue could enter into a state of vicious positive feedback. More hints of a central role for mitochondria in inflammation are beginning to unfold with the recent report of the MAP kinase-p38 axis in sepsis induced inflammation. Mice that are negative for MKK3 (the upstream effector of p38) exhibited reduced NF-κB and inflammasome activity in response to LPS. In the normal setting, mitochondrial ΔΨm is reduced, mtROS is elevated, and ATP levels fall upon LPS treatment (Srivastava et al., 2015). MKK3 knockout animals are protected from loss of ΔΨm suggesting the activation of p38 MAP kinase pathway elicits inflammatory signals by potentiating mitochondrial dysfunction to engage inflammatory signaling.

Mitochondrial DAMPs also show evidence of involvement in cellular senescence. The term senescence-associated secretory phenotype (SASP) refers to a putative hallmark of senescent cells in regards to their constitutive release of numerous cytokines/inflammatory mediators. In macrophages lacking mtDNA, IL-1β production (an inflammasome mediated cytokine) is attenuated while cells retained capacity to undergo apoptosis. Given that senescent cells are generally regarded as resistant to apoptotic signals, this falls in line with data showing IL-1β stimulated PBMCs resist apoptosis (Mangan et al., 1991) while IL-1β activity (in conjunction with IL-1α) has a role in inducing senescence in target human fibroblasts in a paracrine manner (Acosta et al., 2013). For cells having undergone senescence, the signaling response to growth factors is strongly blunted. However, senesced cells remain metabolically active and secrete pro-inflammatory SASP mediators. Which cytokine/inflammatory

mediator combinations are most prominent depend on cell types or mode of senescence such as replicative versus stress-induced premature senescence (SIPS). For example SIPS induced by proteasome inhibition results in a distinct SASP compared to SIPS induced by oxidative stress (Maciel-Baron et al., 2016).

The role of mitochondrial dysfunction in promoting cellular senescence is continuing to unfold particularly in light of inflammation. In accordance with the role of the activation of inflammasome by mtDNA, the interdependence in calcium and H_2O_2 mediate IL-6 and IL-8 SASP composition has been demonstrated *in vitro*. This changes the tissue microenvironment in a paracrine manner by promoting an invasive environment that can be subdued with calcium chelator or catalase antioxidant (McCarthy et al., 2013). Though the focus of this work did not examine the role of mitochondrial inflammatory molecules (e.g. release of mitochondrial related DAMPs), it is plausible they are also involved given that mitochondria are a major site of calcium regulation and site of ROS stress. As a speculation, the mitochondrial role in senescence mediated inflammatory signaling by modulating SASP is likely more complex and dependent on the context of mitochondrial dysfunction. Recent report suggest that mitochondrial stress induced senescence has a distinct secretory phenotype that lacks IL-1. However, to observe this phenotype, senescence was achieved by depleting cells of mtDNA (Wiley et al., 2016). In the context of mtDNA release and inflammasome activation, the secretory phenotype may yet be distinct from senescent cells completely devoid of mtDNA. Inflammasome appears to have a role in oncogene induced paracrine mediated senescence which indeed involves an IL-1α and IL-1β containing SASP (Acosta, Banito, 2013). Another fascinating report provide evidence that mtDNA mediated DAMPs is capable of triggering antiviral innate immune response. During herpes virus infection, stressed mitochondria releases mtDNA into the cytosol, where it engages with other molecules such as DNA sensor cGAS and promotes stimulator of interferon genes (STING)-interferon regulatory factor 3 (IRF3) axis dependent signaling leading to induction of antiviral gene expression (type I interferons) and thus inhibits viral replication (West et al., 2015). Future work will be necessary to clarify DAMP/mtDNA mediated inflammasome activation from a paracrine/autocrine level in establishing senescence.

7.1. *Mitochondrial DAMPs in COPD*

Bacterial and viral infections e.g. influenza virus, rhinovirus, and respiratory syncytial virus, are among the respiratory pathogens known to cause exacerbations in COPD. In fact, respiratory viral infections account for about 50-70% of acute exacerbations in patients with COPD. COPD exacerbations are often followed by subsequent clinical pulmonary deterioration, including significant declines in forced expiratory volume at 1 second (FEV_1), increased lung inflammation and mucus hypersecretion as well as increased hospitalization or mortality.

A variety of stimuli can activate innate immunity, including pathogen-associated molecular patterns (PAMPs) and DAMPs. PAMPs (e.g., LPS and viral double-stranded RNA) are of microbial origin, whereas DAMPs (e.g., uric acid, extracellular ATP, and heat-shock proteins) are host-intrinsic signals that accumulate with stress. Both PAMPs and DAMPs bind to a series of specific pattern-recognition receptors (PRRs), which are either expressed

on the cell surface, or are present in the cytoplasm, leading to inflammasome activation (Kepp et al., 2011). It has been shown that protein associated DAMPs are increased in COPD patients as well as during its exacerbation (Pouwels et al., 2014a, Pouwels et al., 2015, Zhang et al., 2014). This is consistent with the findings that CS exposure causes DAMPs [e.g., HMGB1, S100A8, dsDNA, and mitochondrial DNA (mtDNA)] inducing innate immune response (Heijink, Pouwels, 2015, Pouwels et al., 2014b). Recent studies have shown that increased mtDNA is considered as a mitochondrial DAMP, which escapes from mitochondria due to impaired mitophagy leading to inflammasome activation (Kepp, Galluzzi, 2011, Nakahira et al., 2011, Oka, Hikoso, 2012). It remains unknown whether senesced cells harbors increased mitochondrial DAMP mtDNA due to impaired mitophagy, which alters innate immune and inflammatory responses to viral infection during COPD exacerbations.

Studies aimed at further deciphering the mitochondrial role in potentiation inflammation in COPD and during its exacerbations in light of mitochondrial DAMPs are expanding. The mtDNA is now recognized as a DAMP. COX-I and COX-II mtDNA is increased in exfoliated cells in saliva of smokers' even decades after smoking cessation (Masayesva et al., 2006). Cigarette smoke induces mtDNA release from neutrophils (via the formation of extracellular histone traps), leading to increased airway inflammation (Heijink, Pouwels, 2015). The role of autophagy in mediating release of mtDNA may occur in more regulated fashion (Nakahira, Haspel, 2011). A reduction in autophagic proteins elevates cytoplasmic mtDNA (Oka, Hikoso, 2012) by mitophagy/mitochondrial disruption by CS in combination with MPTP opening (Naserzadeh et al., 2015) which may be involved in mtDNA release, however, this has not been definitively tested to date. MPTP opening which can occur through Ca^{+2} dysregulation or oxidative stress, leads to cytochrome C release and ATP depletion. Since ATP has a role as a DAMP, release of it extracellularly activates P2 receptors (**Figure 2**). In COPD, extracellular ATP is elevated in BALF and neutrophilic $P2Y_2$ receptors are upregulated in blood (Lommatzsch et al., 2010, Mortaz et al., 2009). A recent study suggests that ATP neutralization or nonspecific P2 receptor-blockade may reverse pulmonary emphysema (Cicko et al., 2010). A role of P2Y14 in stem cell senescence is shown (Cho et al., 2014), suggesting that P2Y may modulate cellular senescence (inflammaging) in COPD. These findings suggest potential therapeutic avenues where targeting P2 receptor with antagonists might quells COPD progressing.

8. Summary

Mitochondrial dysfunction associated with aging, and together with chronic smoking, may increase the risk of developing a state of progressive inflammation in the lung. The nature of inflammatory diseases is such that they can become damaging or chronic once they pass the threshold of inflammation resolution. Factors that may be involved in promoting the inflammatory conditions for disease progression may involve mitochondrial DNA/DAMPs and ROS/RSS (**Figure 5**). Attempts to find therapies to halt the exacerbation of chronic inflammatory lung diseases have not been fruitful. Mitochondrial dysfunction in the face of anti-inflammatory regimens continues to persist. Experiments in other tissues reveal a role for mitochondrial mediated inflammation (inflammaging) in a disease setting with current studies underway to assess the efficacy of new mitochondrial targeted therapies. It is not

well understood how mitochondrial mediated inflammation contributes to disease progression. Mitochondrial dynamics are highly complex and their role in regulating inflammation will be necessary to implement control over them. As mitochondria are a unifying factor amongst many diverse cell types, each cell type utilizes mitochondrial functions in different ways. Impairing apoptosis in one cell type may mitigate mitochondrial inflammation whereas the same treatment could exacerbate inflammation in another. Targeting mitochondria to reverse the inflammation in the clinic is a challenge. The limitations to therapy can only be overcome by future basic science discoveries using novel *in vitro* and *in vivo* models that meld towards the development of new approaches for halting disease progression, in particular transfer of MDVs and fresh mitochondria to senesced cells via Miro1 GTPase dependent pathway. The accumulation of conflicting reports in targeting ROS as a therapeutic strategy suggests there is too much of a “butterfly effect” risk by using antioxidants alone without considering dose in combination with treatment time courses. Specific mitochondrial antioxidants (mitoQ) or peptides (SS31) may be beneficial in context with progression of COPD. It has been recently shown that NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice (Zhang et al., 2016). This may have implications for defective mitophagy via impaired fission and fusion. As can be inferred from this review and others, there are many aspects of mitochondrial dysfunction in inflammaging that must be studied within the subtle contexts of redox status of the cells/mitochondria, dynamics, dysfunction/biogenesis, DAMPs, and cellular senescence in the pathogenesis of COPD and during its exacerbations.

8. Future Directions

There are several emerging areas on mitochondrial redox system, dynamics, and dysfunction in lung inflammation and cellular senescence which are discussed and require further research. Some of the key aspects are-

i) How do the mitochondrial quality control (elongation, fission and fusion) mechanisms that are influenced by oxidative stress/redox cellular status impact on overall inflammation and cellular senescence?

ii) How does mitochondrial dysfunction contributes to the pathogenesis of COPD and its exacerbations via pathogenic stimuli (e.g. during viral and bacterial infections via DAMPs)?

iii) It is not clear the role of mitochondrial signaling events in regulation of the telosome, shelterin, and hence cellular senescence, which is a target area for future research and therapeutic approaches in conditions like COPD and age-related diseases.

iv) Role of mtROS and RSS in establishing cellular senescence and senescence phenotype via mitochondrial dysfunction will lead to future therapeutic strategies based on mitochondrial dysfunction.

v) Glycosis and TCA cycle metabolites, such as succinate and lactate may have effects on inflammation and cellular senescence, and hence studies should be

directed toward understanding the mitochondrial metabolome in context with age-related diseases, such as COPD.

vi) Future research can be directed to study mitophagy inducers (e.g., Pink1 and Parkin activators), removal of defective mitophagy, and/or intercellular transfer of fresh/healthy mitochondria and/or pharmacological manipulation Rho-GTPase Miro1 for the management of these debilitating diseases.

vii) Protection of mitochondria by its transfer into the damaged lung epithelial cells through Miro1-dependent signal against CS-induced mitochondrial dysfunction, and cellular senescence have translational potential, as it will characterize mitophagy, understand the mechanism of telomere shelterin (telosme) complex disruption, and mitochondria transfer as the therapeutic targets for not only attenuating mitochondrial dysfunction and perinuclear clustering during stress, but also protecting lung cells against cellular senescence.

viii) Characterization of nanotubes via Miro1 transfer of mitochondria will provide biochemical and molecular signaling mechanisms for attenuating dysfunctional fresh mitochondria transfer into senesced cells.

Overall, understanding the points discussed above will provide translational potential on attenuation of telomere shelterin complex (telosome)/cellular senescence based on understanding the mechanism and/or Miro1-mediated mitochondria transfer in attenuating CS-induced dysfunctional mitochondria in the development of COPD/emphysema. This will reveal new directions for research based on understanding mitochondrial function, redox system, targeting mitophagy (including the shelterin complex) and mitochondria transfer in lungs of COPD/emphysema.

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Abbreviations

AMPK	AMP-activated protein kinase
COPD	chronic obstructive pulmonary disease
COX	cytochrome c oxidase
CS	Cigarette smoke
DRP1, DNM1L	dynamin 1-like
Δψm	mitochondrial membrane potential
ETC	electron transport chain
FIS1	fission 1

H2O2	hydrogen peroxide
LC3	microtubule-associated protein light chain 3
MDVs	mitochondria-derived vesicles
Mfn	mitofusin
MPTP	mitochondrial permeability transition pore
mtDNA	mitochondrial DNA
mtROS	mitochondrial reactive oxygen species
mtDAMP	mitochondrial damage associated molecular patterns
O2.−	superoxide anion
OPA1	optic atrophy 1
PINK1	PTEN-induced putative kinase 1
PRRs	pattern-recognition receptors
SASP	senescence-associated secretory phenotype
SIPS	Stress induced premature senescence

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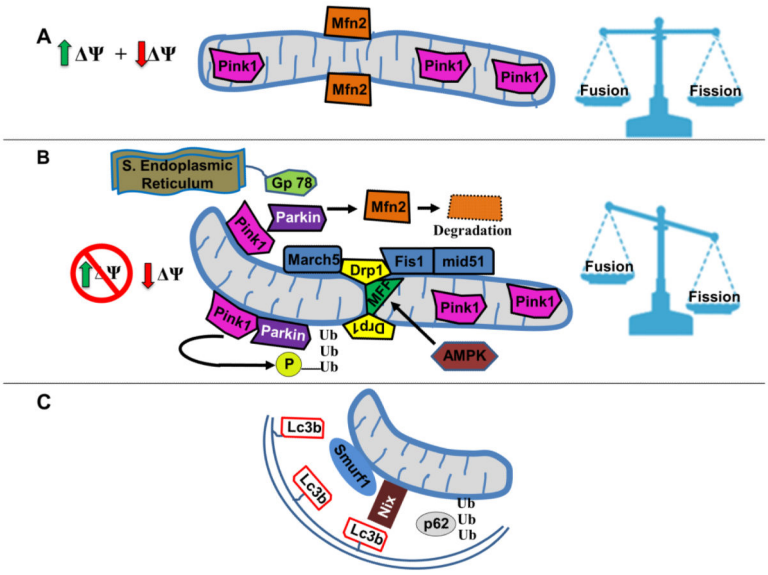

Figure 1. Mitochondrial function maintained by mitophagy

Reduced mitochondrial membrane potential in Parkin competent cells stimulates Drp1 fission. **A**) Homeostasis: In cells unchallenged by excessive stress, fission and fusion occurs at basal level. Most mitochondria are polarized and maintain Pink1 import into the inner mitochondrial membrane. **B**) Stress: Substantial loss of mitochondrial membrane potential promotes fission. Pink1 stabilization on the outer membrane (OM) recruits the E3 ligase Parkin. The E3 ligase Gp78 which is associated with smooth endoplasmic reticulum membranes is activated independently of Parkin to promote fission. Both Parkin and Gp78 potentiates the degradation of mitochondrial fusion proteins mitofusin 1 and mitofusin 2 (MFN 1/2). AMPK activates mitochondrial fission factor (MFF) to recruit Drp1 mediates membrane “constriction” at the site of fission through its GTPase activity. MARCH5 is a mitochondrial E3 Ligase that promotes Drp1 along with Fis1 and mid51. Parkin also catalyzes the ubiquitination of OM mitochondrial proteins. Pink1 phosphorylates ubiquitin leading to Parkin activation which is involved in the mitophagy induction process. **C**) Mitophagy: Depolarized mitochondria are unable to fuse back into the function pool of mitochondria. Scaffolding protein p62 binds to OM ubiquitin in addition to Smurf1, and Nix, to facilitate mitochondria targeting to LC3b coated autophagosomes.

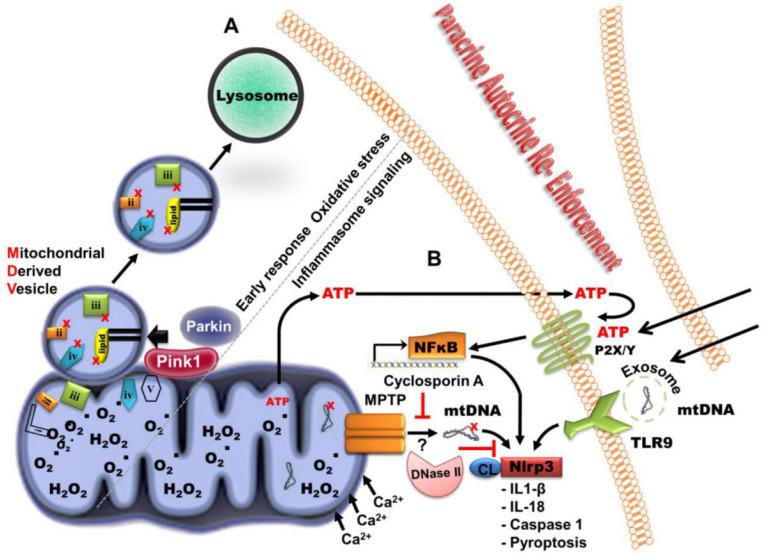

Figure 2. Mitochondrial stress mediated mitochondrial derived vesicle (MDV) formation and activates inflammasome

A) Prior to mitophagy, oxidative stress and loss of mitochondrial membrane potential recruits Parkin to mediate mitochondrial derived vesicle (MDV) formation. MDVs load oxidized protein and lipid constituents for delivery into the lysosome. MDVs are mitochondrial derived cargos that contain selective proteins involved in electron transport chain (ETC). Oxidized lipids and ETC proteins of complexes II, III, and IV are targeted for MDV mediated degradation. **B**) During mitochondrial stress, damage to mitochondria can lead to calcium influx and opening of the mitochondrial permeability transition pore (MPTP). Opening of MPTP is correlated with release of mitochondrial mtDNA. Oxidized mtDNA binds to the Nlrp3 inflammasome interacting with mitochondrial derived cardiolipin (CL). This stimulates its activation and release of inflammatory mediators IL1-β and IL-18. Inflammasome is also able to promote pyroptosis, a highly inflammatory type of cell death. Pyroptosis occurs through Caspase-1 mediated events which may further amplify release of inflammatory damage associated molecular patterns (DAMPS) and perpetuate inflammation throughout the tissue. Released ATP acts as a DAMP through purinergic receptor signaling (P2X/Y) and transactivates NFκB expression further enhancing inflammasome activation. Extracellular mtDNA released from damaged cells or may be enclosed in exosomes bind to and stimulate Toll-like receptor (TLR) signaling to Nlrp3. These pattern recognition receptors PRRs integrate extracellular damage signals that converge on mitochondrial mediated inflammatory response. DNase II has a role in regulating Nlrp3 signaling and through mtDNA digestion. Oxidized lipids, ETC proteins and mtDNA are marked in red color with “X” symbol.

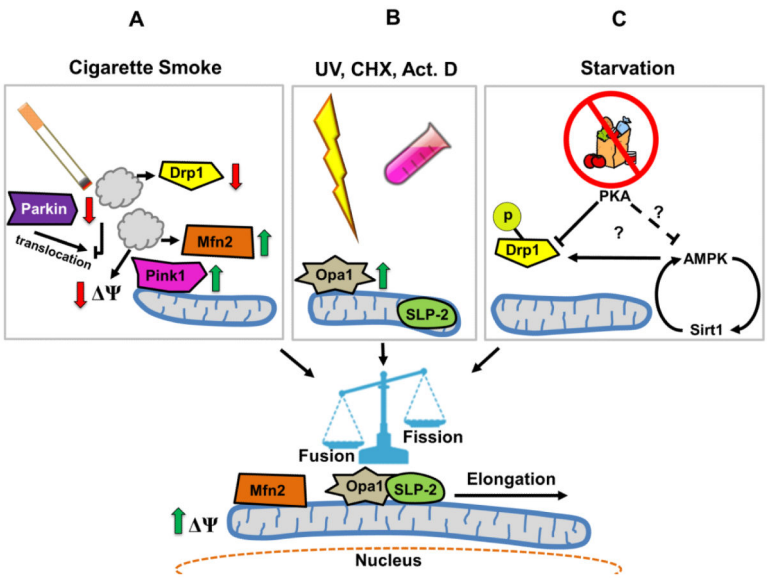

Figure 3. Elongation of mitochondria as a survival mechanism

Perinuclear enrichment of elongated mitochondria under different stress responses, allows cell survival when mitophagy is disrupted. It is thought this stress response potentially protects a portion of mitochondria against excessive mitophagy. **A**) Cigarette smoke exposure impairs Parkin translocation to mitochondria which is associated with impaired mitophagy while promoting increased levels of fusion protein Mfn2 and a reduction in fission protein Drp1. Parkin may not be able to promote fission by potentiating Mfn2 degradation. **B**) Ultraviolet light, Cyclohexamide, and Actinomycin D induced mitochondrial elongation is a SLP-2 dependent manner. Stabilization of SLP-2 on the outer mitochondrial membrane following stress, results in stabilization of the long form Opa1 fusion protein. **C**) Nutrient starvation activates Protein Kinase A to phosphorylate fission protein Drp1 and inhibit its activity. AMPK has been shown to promote Drp1 activity which may involve regulation by PKA and Sirt1 activity. During starvation induced stress, AMPK promotes NAD^+ levels which can function to enhance AMPK by Sirt1 mediated deacetylation. Evidence that PKA can also block AMPK activity as well suggests a hypothetically a level of control may occur here to promote the ideal amount of mitochondrial fusion and elongation. Elongation following starvation upholds ATP production in the cell by maintaining membrane potential and hence elongated mitochondria appear to be resistant to mitophagy.

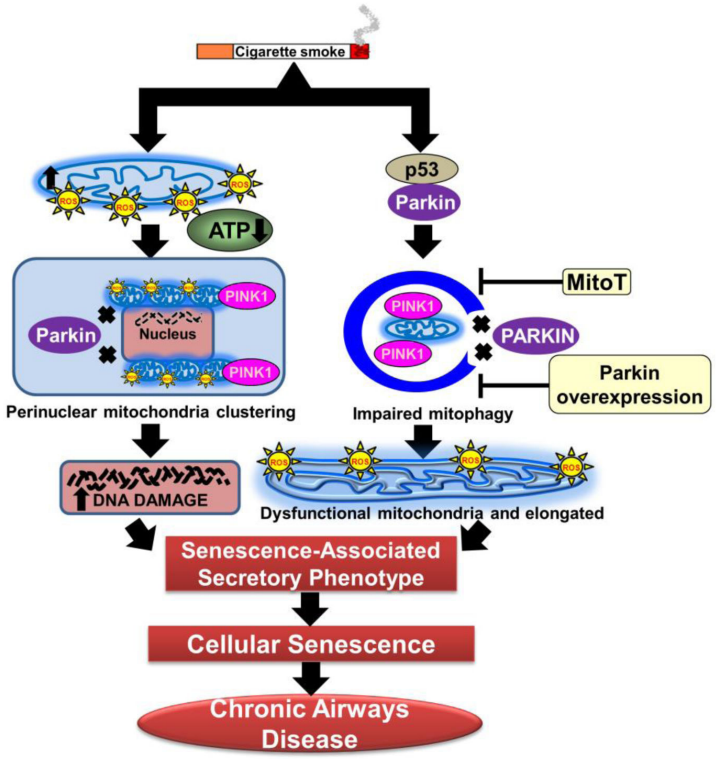

Figure 4. Cigarette smoke-mediated mitochondrial dysfunction is due to impaired mitophagy leading to cellular senescence in COPD

This schematic is based on our recent report that CS-induced oxidative stress causes reduction in cellular ATP levels and increase in ROS along with mitochondrial dysfunction thereby activating Pink1-Parkin mediated mitochondrial fusion (Mfn2) leading to perinuclear clustering of dysfunctional mitochondria (elongated). This process is accompanied by increase in DNA damage-initiated cellular senescence. Cigarette smoke exposure affects Parkin and p53 interaction, as a result impairs Parkin-dependent mitophagy process and increases perinuclear mitochondrial clustering. Mitophagy impairment and cellular senescence phenotype was considerably rescued by Parkin overexpression along with MitoT treatment. This observation supports the notion that molecular mechanisms of mitophagy play an essential role during CS stress-induced cellular senescence via suborganellar signaling in COPD.

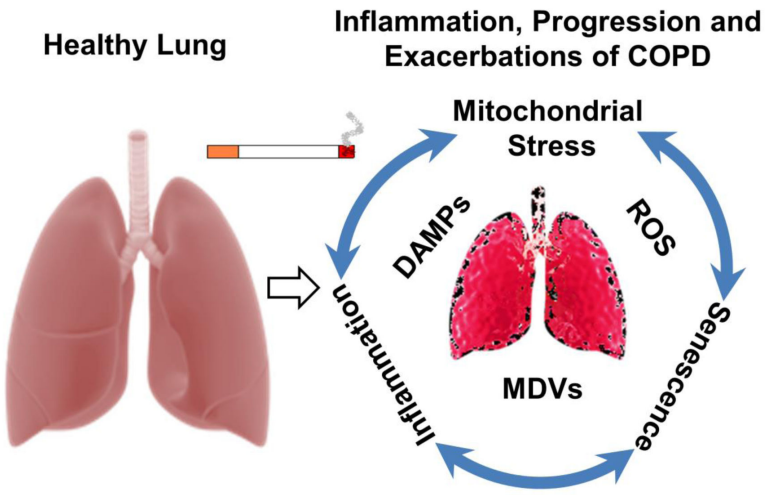

Figure 5. Mitochondrial Stress in COPD

Inflammation is strongly associated with progressive lung diseases such as chronic obstructive pulmonary disease (COPD). **Healthy lung:** There are over 40 different lung cell types including infiltrating leukocytes that maintain tissue homeostasis. Lung parenchymal and immune cell communication in response to endogenous or environmental stress (bacterial and viral infections, smoking, air pollution) relay inflammatory signals between each other. The inflammatory signals that are critical to tissue repair and pathogen defenses achieve resolution from an inflammatory state and retain respiratory function. **Inflamed lung:** In lung disease, respiration is comprised in chronic and progressive chronic lung diseases (COPD). Mitochondria are central in mediating respiration and recent findings support that mitochondrial stress and dysfunction correlates with chronic airway diseases. This schematic introduces mitochondrial stress and dysfunction plays a key role in the inflammatory state associated with chronic lung diseases. Oxidative stress causes release of damage associated molecular patterns (DAMPS) from dysfunctional mitochondria and damaged cells. The contributing role of exosomes in the pathogenesis of chronic lung diseases is an emerging theme that needs to be explored. Together, the chronic mitochondrial stress would enable a vicious cycle that relentlessly promotes disease state (tissue remodeling, inflammatory cellular influx, senescence, susceptibility to infection). Current anti-inflammatory regimens do little to reverse disease progression. This may be due to the persistence of inflammatory signaling by abnormal mitochondria. Therefore, therapies that effectively target and improve mitochondrial function throughout the lung might be critical in taking steps towards blocking damaging inflammatory processes including exacerbations that further harm the tissue.