

Mitochondrial alterations during oxidative stress in chronic obstructive pulmonary disease

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Abstract: The high incidence of chronic obstructive pulmonary disease (COPD), one of the most prevalent diseases worldwide, has attracted growing attention. Cigarette smoking is considered a major contributory factor in the pathogenesis and progression of COPD due to the tremendous oxidative burden that it causes, which induces an oxidant/antioxidant imbalance. Excessive oxidation induced by the excessive generation of mitochondrial reactive oxygen species disturbs the antioxidant systems and plays an important role in triggering and promoting chronic inflammation of airways. Given that mitochondria is one of the main sites of reactive oxygen species production by the oxidative phosphorylation process, oxidative stress may affect mitochondrial function by changing its structure and morphology and by affecting a series of mitochondrial proteins. In particular, PTEN-induced putative kinase 1/Parkin and p62 play critical roles in mitophagy. During the process, the Akt ubiquitin E3 ligase is an important mediator associated with cigarette smoke exposure-induced pulmonary endothelial cell death and dysfunction. Thus, understanding the underlying mechanisms of the signaling pathway may provide important information regarding the therapeutic treatment of COPD by application of alternative PTEN-induced putative kinase 1 targets or ubiquitin E3 ligase.

Keywords: chronic obstructive pulmonary disease, reactive oxidative stress, reactive nitrogen stress, mitochondrial fission/fusion, mitophagy

Introduction

Chronic obstructive pulmonary disease (COPD), an inflammatory disease with rising incidence worldwide, is characterized by sustained airflow limitation and is always associated with pulmonary arterial hypertension, hypoxemia, and hypercapnia, which significantly increases the likelihood of cardiopulmonary complications and aggravates the patients' conditions. A survey showed that about 65 million people have COPD globally, and almost 3 million people, majorly from low- and middle-income countries, died of complications associated with COPD in 2005.¹

With regard to the causes of the development of COPD, various studies have proven that oxidative stress induced by reactive oxygen species (ROS) plays a major role in triggering and promoting chronic inflammation of airways and imbalances in protease/antiprotease activity.² Cigarette smoking is one of the most important risk factors that contain a large amount of ROS that induce an oxidant burden in smokers,^{3–7} affecting the oxidant–antioxidant mechanisms in the development of COPD.⁸ Exposure to cigarette smoke induces the production of endogenous ROS as a byproduct of functional electron transfer chain in the mitochondria.⁹ Mitochondria is a crucial semiautonomous cellular organelle housing the metabolic processes of oxidative phosphorylation and fatty acid metabolism, and is also a tool bridging signal transduction between the nucleus and extracellular threats. Despite the fact that

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mitochondria is one of the main sources of endogenous ROS, mitochondrial dysfunction has been found in oxidant-induced lung damage due to the susceptibility of mitochondrial DNA to oxidative damage, which consists of a reduction in mitochondrial biogenesis.^{10,11} Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), a central integrator of multiple signaling pathways, has been demonstrated to play a key role in the regulation of mitochondrial biogenesis and oxidative stress by a mitochondrial transcription factor A (TFAM).¹² These signaling factors regulating mitochondrial biogenesis are increased in COPD muscle, leading to a low muscle oxidative capacity in COPD.^{10,13}

Oxidative stress affects not only mitochondrial biogenesis, but also the mitochondrial quality control in the pathogenesis of lung diseases.¹⁴ A previous study indicated that ROS induced by cigarette smoke were involved in the alterations in mitochondrial network morphology.¹⁵ Additionally, in the airway smooth muscle (ASM) from patients with an airway disease, mitochondria exhibited substantial morphologic defects and the balance between mitochondrial fission and fusion was disturbed. Similar alterations have also been observed in the

mitochondria in airway epithelial cells of COPD patients exposed to chronic cigarette smoke.¹⁶ Overall, mitochondria seem to play an important role in different aspects of cellular structure and function, as well as in ROS induced by alterations of mitochondrial morphology. However, the molecular mechanisms between the mitochondria-induced ROS and the pathologic process of COPD have not been fully understood. Thus, this review aims to discuss how oxidative stress affects the progression and pathogenesis of COPD, and the corresponding alterations in mitochondria-mediated structures in response to oxidative stress have also been reviewed.

Source of ROS

Oxidation is a chemical process in which electrons are removed from molecules; during the process, the leaked electrons contribute to generation of some highly reactive free radicals. Generally speaking, the accumulated ROS are derived in two ways: exogenous and endogenous ROS (Figure 1). Exogenous ROS primarily originate from inhaled toxic gases or environmental pollutants such as car exhaust fumes, occupational exposure to dusts and cigarette smoking.

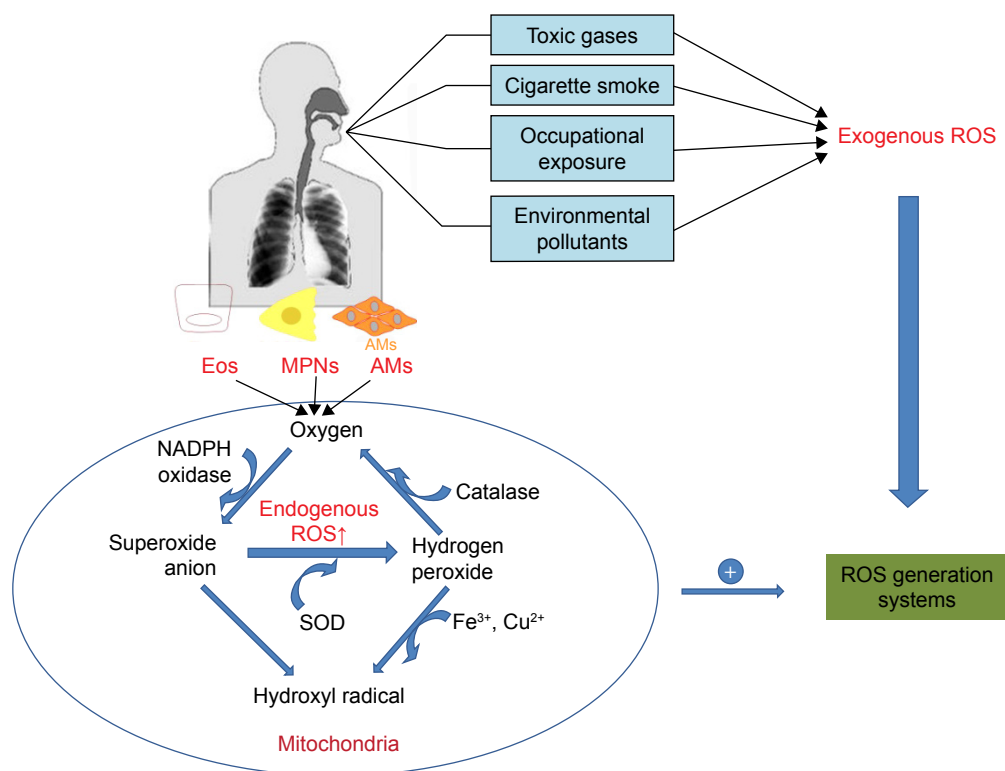


Figure 1 Sources of ROS in vivo.

Notes: Toxic gas, cigarette smoke, occupational exposure and environmental pollutants are the major sources of exogenous ROS that result in lung injuries in COPD. Alveolar macrophages, eosinophils and epithelial cells are damaged by interacting with inhaled oxidants, activating various relevant enzymes such as SOD and catalase to convert the oxygen inhaled to another forms of ROS, which contributes to the endogenous ROS in vivo. Initiating by endogenous and exogenous stimulus, the ROS-generating systems can be activated via the redox-sensitive pathway.

Abbreviations: COPD, chronic obstructive pulmonary disease; ROS, reactive oxidative species; SOD, superoxide dismutase; Eos, eosinophils; MPNs, polymorphonuclear cells; AMs, alveolar macrophages.

The sources of endogenous ROS include mitochondrial respiration, peroxisomes, the NADPH oxidase (NOX) system and inflammatory cells,¹⁷ while the oxidative phosphorylation process in the mitochondria is one of the major sources of endogenous ROS.^{9,18}

Peroxisome is a source of endogenous ROS, especially hydrogen peroxide (H_2O_2) and superoxide anions (O_2^-). For example, a heme-containing peroxidase in neutrophils and monocytes, myeloperoxidase, correlates with an increased level of ROS and chronic inflammation in COPD patients.^{19,20} Inflammatory cells also contribute to the formation of endogenous ROS under the catalysis of intracellular enzymes such as NOXs, ubiquinone reductase and cytochrome oxidase, while NOXs have long been recognized to be one of the primary generators of ROS within the lung and play pivotal roles in the pathogenesis of a number of diverse chronic lung disorders.^{21,22} NOX enzymes catalyze the conversion of O_2 into O_2^- , which is a reactive radical characterized by its speedy interaction with intracellular macromolecules (lipids, proteins and DNA). There are seven members of NOXs: NOX1–5, dual oxidase DUOX1 and DUOX2. The expression levels of DUOX1 and DUOX2 that are primary expressed in the barrier epithelia were found to be low in the airway epithelium of former smokers with mild/moderate COPD.^{23,24} NOX1 mRNA expression was increased in patients with COPD, which contributes to rhinovirus infection-related exacerbations.²⁵ Pulmonary vascular endothelial cells have been shown to produce ROS in the presence of NOX2.²⁶ NOX3 in the lung was found to be associated with lung destruction and emphysema in aged mice with TLR4 deletion, but these effects were reversed on treatment with NOX inhibitors.²⁷ The ability of NOX4 to generate ROS has also been verified. An increasing number of researches have revealed that an increased expression of NOX4 was observed in pulmonary diseases.^{28–31} Recently, Hollins et al found that the expression of NOX4 was increased in ASM in COPD both in vivo and in primary cells in vitro.³² Liu et al also showed NOX4 protein was increased in the ASM, and its expression correlated positively with disease severity and inversely correlated with the pulmonary functions in COPD patients.³³ Inhibition of NOX4 expression increased the mitochondrial TFAM level, leading to stimulation of mitochondrial biogenesis.¹² Oxidative stress induced by abundance of ROS can affect the organelles and disrupt cellular homeostasis.

Mitochondria are one of the main sources of production of ROS in eukaryotic cells. The production of ROS is a consequence of electron leakage occurring in the mitochondrial

electron transport chain. During aerobic respiration, high-energy electrons pass through electron carriers in the respiratory chain complexes and react with molecular oxygen to form O_2^- , primarily at complexes I and III. This process is responsible for the generation of adenosine triphosphate (ATP), which promotes pumping of protons from the mitochondrial matrix into the intermembrane space, creating a measurable electrochemical proton gradient. However, protons are pumped back into the matrix in the presence of ATP synthase and react with the O_2^- in a reaction catalyzed by superoxide dismutase, contributing to the formation of hydrogen peroxide.³⁴ Superoxide at a high concentration causes oxidative damage. The formed H_2O_2 may give rise to hydroxyl radicals or is decomposed into water and oxygen by catalase. Therefore, the presence of O_2^- plays an important role in the formation of other forms of ROS. Excessive levels of mitochondrial ROS degrade the mitochondrial function and lead to the collapse of electrochemical gradient, which leaves the cell more susceptible to ROS-mediated injury.³⁵ Given that oxidative stress in COPD patients is a prevailing phenomenon, we next reviewed how oxidative stress induced by excessive ROS plays a role in the pathogenesis of inflammation in COPD.

The role of oxidative stress in COPD pathogenesis

Minutoli et al³⁶ and Park et al³⁷ suggested that accumulation of mitochondrial ROS activates inflammatory pathways in various tissues by interfering with mitochondrial quality control. Evidence shows that excessive mitochondrial ROS causes oxidative damage, which was reflected by the increased levels of damaged proteins, DNA and lipids in the mitochondria, as well as inflammatory markers within the cells in COPD patients.³⁸ Actually, ROS exhibit their toxic properties under specific conditions when the anti-oxidant system fails to eliminate excessive free radicals. In this case, gaseous-phase ROS in inhaled irritants cause direct damages to airway epithelial cells and their plasma cell membranes when its level exceeds the scavenge ability of the cellular anti-oxidative system.³⁹ Thus, antioxidant defense systems, including the nuclear factor-erythroid-2-related factor 2 (Nrf2)-mediated antioxidant system (Figure 2) and the phase II detoxifying enzymes, are attenuated by excessive accumulation of ROS. Denuded epithelia are always observed in COPD, increasing the possibility that the ROS can reach the ASM and promote the proliferation of ASM (Figure 3), leading to thickening of the airway walls and an accelerated decline in lung function.⁴⁰

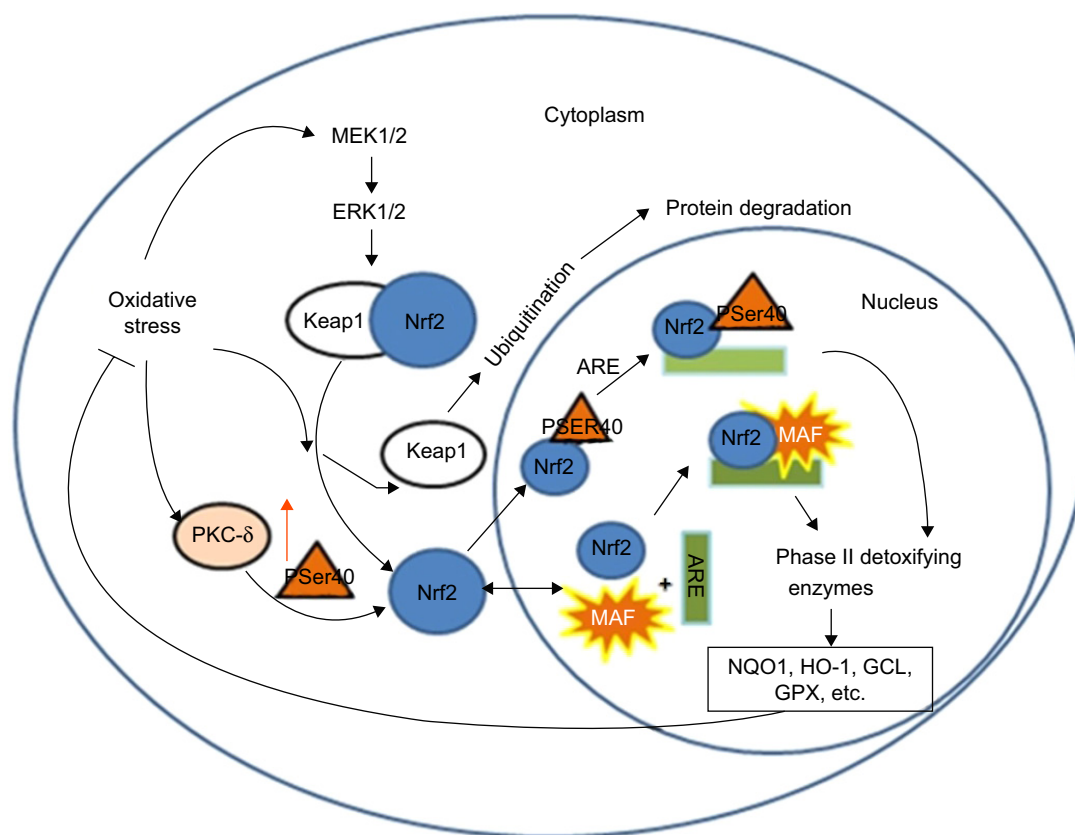


Figure 2 Antioxidant mechanisms of stress sensing in Nrf2-mediated system.

Abbreviation: Nrf2, nuclear factor-erythroid-2-related factor 2.

Inflammatory cells such as CD8⁺ T lymphocytes, neutrophils and alveolar macrophages are stimulated on exposure to oxidative stress, which affects the pulmonary epithelial cells.⁴¹ One of the most obvious alterations in the inflammatory process is the imbalance of the protease/antiprotease system within the respiratory system, which promotes the release of the proteolytic enzymes of neutrophils and macrophages (matrix metalloproteinase-12), thus contributing to the degradation of their natural inhibitors. Consequently, the pulmonary parenchyma is destroyed, which accounts for the emphysema. During this process, accumulation of neutrophil elastase, a potent serine proteinase and a key effector that is most likely responsible for the emphysema, has been found in COPD patients.⁴² Moreover, neutrophil elastase upregulates the levels of interleukin (IL)-8 and mucin 5AC that is a glycoprotein linked to mucus hypersecretion in the pulmonary tract. In bronchial epithelial and alveolar cells, ROS also induce the gene expression of inflammatory mediators such as tumor necrosis factor (TNF)- α , which in turn activates the transcription of IL-8, matrix metalloproteinase-9, mucin 5AC as well as interferon- γ .^{43–46} Several mechanisms such as TNFRs, NLRP3 inflammasome signals and MAPK are

responsible for the mitochondrial ROS-mediated inflammatory responses. Bulua et al stated that mitochondrial ROS promote the production of proinflammatory cytokines including IL-6 and TNF in the cells from patients with TNFR1-associated periodic syndrome.⁴⁷ Levels of IL-1 β and IL-18 are increased by the NLRP3 pathway. However, redox-sensitive transcription factors including NF- κ B and AP-1 regulate these inflammatory genes' expression.

Alterations of mitochondrial morphology in COPD

Recently, alterations in mitochondrial morphology are thought to be involved in oxidative stress in COPD pathology. The structural changes of mitochondria are closely linked to oxidative stress-mediated signaling. Cigarette smoke induced mitochondrial fragmentation and damaged their networked morphology in nonasthmatic human ASM cells, which depended on the level of oxidative stress.¹⁶ However, cigarette smoke-triggered oxidative stress at a mild level induced mitochondrial hyperfusion in alveolar epithelial cells, which renders the cell more vulnerable to additional stress.⁴⁸ Furthermore, cigarette smoke-induced mitochondrial hyperfusion diminished mitochondrial quality control and impaired

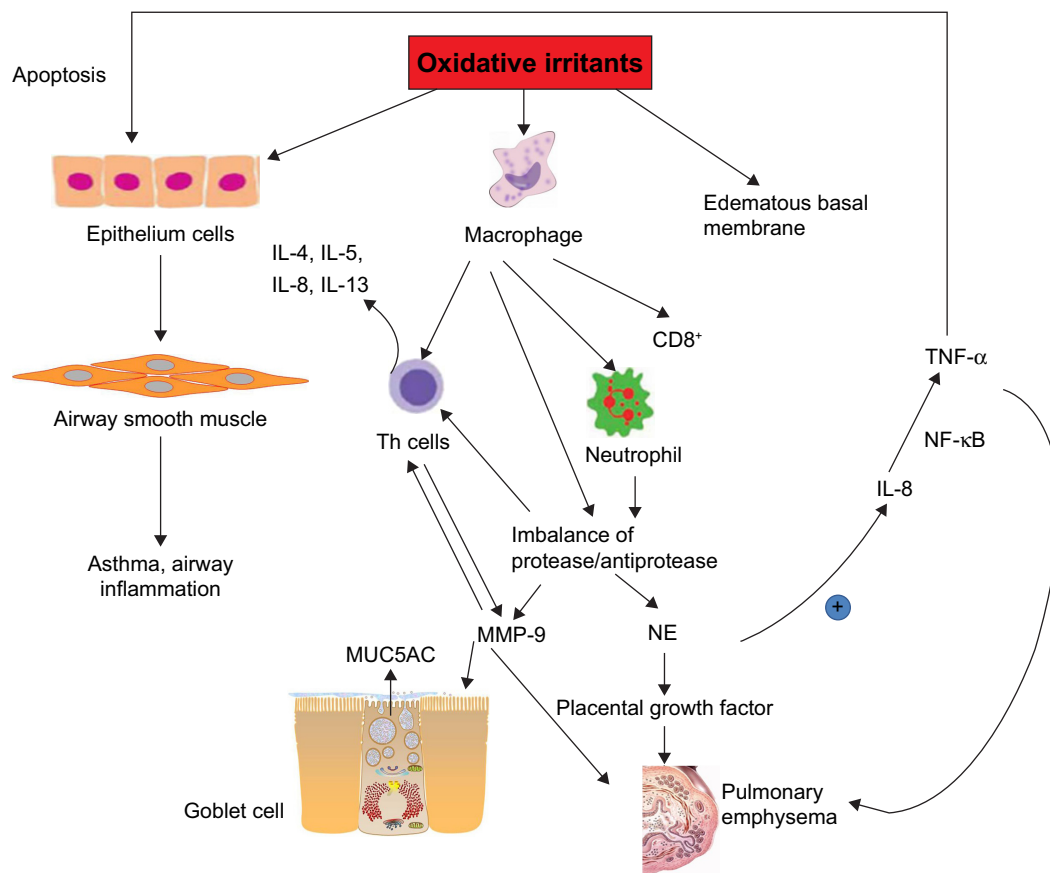


Figure 3 Mechanisms of oxidative stress injuries in COPD.

Notes: Oxidative irritants including tobacco smoke directly affect the epithelial cells, macrophages, and edematous basal membrane. The ASM markedly increases under excess exposure of ROS. The activated macrophage passes oxidative signaling to neutrophils and Th cells, which causes imbalance in protease/antiprotease system and overexpressions of MMP-9 as well as NE. The increased expression of NE induces the TNF- α by the NF- κ B signaling pathway, which accelerates apoptosis of epithelial cells.

Abbreviations: ASM, airway smooth muscle; COPD, chronic obstructive pulmonary disease; IL, interleukin; MMP, matrix metalloproteinase; MUC5AC, mucin 5AC; NE, neutrophil elastase; ROS, reactive oxygen species; TNF, tumor necrosis factor.

cellular stress resistance and cellular senescence, contributing to age-related COPD pathogenesis.

Thus, it is necessary to understand how the mitochondrial morphology is altered in response to the cellular stress induced by ROS in the progression of COPD.

To provide protection against severe cellular stress, mammalian mitochondria are not static structures, but undergo frequent shape changes to form tubular, reticular or networked morphology by changing mitochondrial fission/fusion. Both mitochondrial hyperfusion and mitochondrial fragmentation are a part of the mitochondrial quality control to maintain robust mitochondrial function for impaired mitochondria, while mitochondrial fusion is an adaptive stress-resolving mechanism that involves exchanging the damaged mitochondrial DNA, lipids or proteins with those of healthy mitochondria.⁴⁹

Mitochondrial fusion leads to elongated mitochondria in order to eliminate defective mitochondrial components.⁵⁰ During this process (Figure 4), three large guanosine triphosphatases (GTPases), including mitofusion (Mfn) 1 and 2

embedded in the outer membrane of mitochondria and fusion protein (optic atrophy protein 1 [Opa1]) on the inner membrane of mitochondria, are of particular interest in morphologic maintenance. In fact, Opa1 and Mfns share a reciprocal relationship. The evolutionarily conserved GTPases, Mfn1 and Mfn2, are responsible for outer mitochondrial membrane fusion,⁵¹ while the pro-fusion effect of Mfn1 is promoted by the binding to guanine nucleotides to protein- β subunit 2 (G β 2), thus facilitating and stabilizing clustering of Mfn1 on the outer mitochondrial membrane.⁵² Furthermore, the effects of Mfn2 are attributed to the expression of PGC1- α and PGC1- β .⁵³ The dynamin-related GTPase, Opa1, mediates inner membrane fusion, and depletion of this protein results in severely reduced respiratory efficiency.⁵⁴ The effects of these three proteins have been proven by mouse knockout studies, which provided clear evidence of reduced mitochondrial fusion as an adaptive mechanism of resolving cellular stress in the cells.^{55–57} Hoffmann et al¹⁶ suggested that cigarette smoke induced morphologic changes in the COPD epithelium by significantly increasing the expression

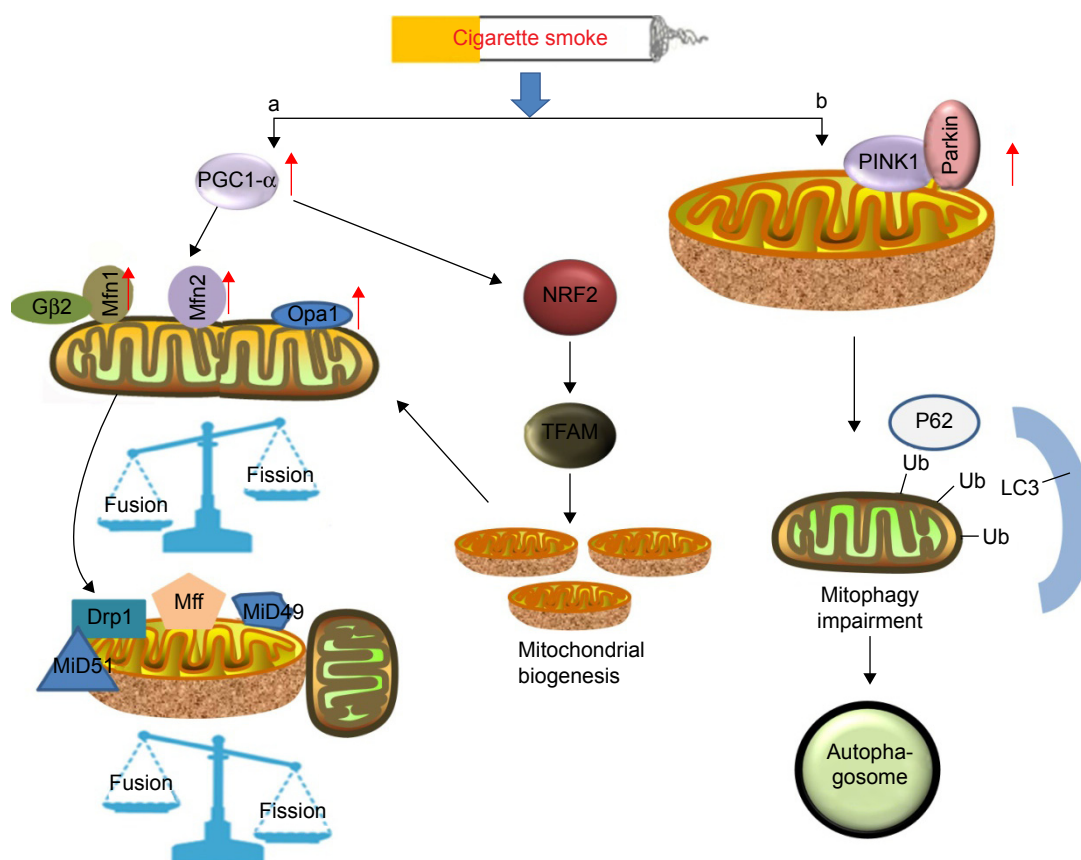


Figure 4 Schematic diagram shows that cigarette smoke induces mitochondrial fusion/fission and mitophagy.

Notes: (a) Cigarette smoke causes mitochondrial fusion in response to mild stress by increasing the accumulation of Mfn1/2 and Opa1. Mitochondrial fission occurs in response to increased ROS. (b) When the depolarized or fragmented mitochondria are unable to fuse back into the functional pool of mitochondria, PINK1 accumulates on the mitochondrial membrane and recruits the E3 ligase Parkin. Parkin conjugating with Ub mediates the degradation of mitofusins 1 and 2. P62 binds to the outer membrane Ub to facilitate mitochondria targeting to LC3.

Abbreviations: Mfn, mitofusion; Opa1, optic atrophy protein 1; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; Ub, ubiquitin.

of Mfn1/2 and Opa1, which were accompanied by increased levels of the proinflammatory mediators such as IL-8, IL-6 and IL-1 β . Such a phenomenon of mitochondrial hyperfusion was also observed in the alveolar epithelial cells on exposure of cigarette smoke, which renders the cells more vulnerable to additional stress.⁴⁸ Furthermore, cigarette smoke-induced mitochondrial hyperfusion diminished mitochondrial quality control and impaired cellular stress resistance and cellular senescence, contributing to age-related COPD pathogenesis. Ahmad et al have shown that cigarette smoke extract induced elongated mitochondria and reduced ATP levels in lung epithelial cells and fibroblasts.⁵⁸ Mitochondrial fusion is a common phenomenon in mitochondria exposed to mild oxidative stress, whereas mitochondrial fission accelerates cellular necroptosis.¹⁵

Accordingly, mitochondrial fission is highly correlated with cell apoptosis and mitophagy. Mitochondrial fission is achieved by phosphorylation of Drp1 at Ser616, which promotes the recruitment of Drp1 from the cytosol to the

mitochondrial surface, by human fission protein-1, mitochondrial fission factor and mitochondrial dynamics proteins of 49 and 51.^{14,54} The possible mechanism indicates that oxidative stress increases the expression of the TFAM protein, thus triggering mitochondrial fission and loss by enhancing Drp1 translocation from the cytosol. Cigarette smoking-induced mitochondrial ROS accelerates the course of phosphorylation of Drp1.¹⁵ However, inhibition of Drp1 significantly increases Bad S112 phosphorylation, which acts against fission-mediated apoptotic cell death.⁵⁹ Additionally, a prolonged exposure of cigarette smoke in COPD patients also significantly induces the expression of Fis1 and decreases the levels of Mfn1/2 and Opa1 on the airway epithelial mitochondria,⁵⁹ indicating that ROS contribute to mitochondrial fission. Mitochondrial fragmentation has further been described in the ASM cells of patients with COPD.⁶⁰ ASM cells cultured from a restricted group of COPD patients showed a collapsed mitochondrial membrane potential, an increased expression of mitochondrial fission protein and

reduced respiratory complex protein, and accumulation of mitochondrial ROS, which contribute to the development of airway hyperresponsiveness and lung inflammation.⁶⁰ Moreover, Aravamudan et al also demonstrated that cigarette smoke induced mitochondrial fragmentation and damaged their networked morphology by increased expression of Drp1 and decreased Mfn2 in nonasthmatic human ASM cells, and this process involved ROS.¹⁵ Recently, Wang et al⁶¹ demonstrated that stress-induced mitochondrial fission and apoptosis were mediated by cyclin C-Cdk8 by enhancing the association between Drp1 and mitochondrial fission factor, which stabilizes their retention on the mitochondria in mouse embryonic fibroblasts. However, whether the same effects of C-Cdk8 are linked to lung disease remains unknown and deserves further investigation.

Mitophagy in COPD

Oxidative stress impairs mitochondrial function. When the depolarized or fragmented mitochondria are unable to fuse back into the functional pool of mitochondria, mitophagy will take place as a protective mechanism by degrading the cellular components to prevent spreading of damage in the mitochondrial network.⁶² The formation of autophagosomes is a consequence of this process.¹⁸ Mitophagy plays a potentially protective role in removal of mitochondria damaged by cigarette smoke.⁶³ A cytosolic E3 ubiquitin ligase Parkin and the PTEN-induced putative kinase 1 (PINK1) that is an upstream regulator of Parkin are stimulated in this process.^{62,64} When the mitochondria are depolarized and fail to regain their membrane potential to protect themselves from detrimental effects, the process of mitophagy begins.⁶² Recent observations have shown that cigarette smoke exposure induces mitophagy, which contributes to overall mitochondrial quality in the epithelial cells and is likely initiated by PINK1 stabilization. The PINK1–PARK2-mediated pathway may account for mitophagy.⁶⁵ Knockdown of PINK1 and PARK2 results in enhanced mitochondrial ROS production and cellular senescence in human bronchial epithelial cells, with insufficient mitophagy of the cells. These findings suggest that defective mitochondria in a cell undergo mitophagy in a PINK1-dependent manner and that PINK is the initiator of this process.⁶⁶

In terms of mechanism (Figure 4), PINK1/Parkin-mediated mitophagy is a complex process involving ubiquitination and autophagy.⁶⁷ Upon dissipation of the mitochondrial membrane potential, Parkin translocates to depolarized mitochondria through phosphorylation at Ser65 in the ubiquitin-like domain (Ubl) by PINK1.⁶⁸ Subsequently, numerous outer

mitochondrial membrane proteins are ubiquitinated by Parkin, which in turn triggers accumulation of other proteins on the mitochondrial surface.^{69,70} In a mechanistic study of the damaged mitochondria, two distinct polyubiquitin chains, linked through K27 and K63 of ubiquitin, were reported to be formed at clustered mitochondria in the presence of Parkin.⁶⁹ Accompanied with the formation of the specific polyubiquitin chains, a molecular weight shift of voltage-dependent anion channel 1 (VDAC1) seemed to be correlated with an increased level of PINK1, indicating that VDAC1 probably participated in PINK1/Parkin-dependent mitophagy. Indeed, it was identified that phosphorylation of VDAC1 is necessary in Parkin-mediated mitophagy, during which the adapter protein p62 exerts a pivotal role in the clearance of damaged mitochondria since Parkin-dependent mitophagy requires p62/SQSTM1/sequestosome-1 recruitment to the clustered mitochondria for final clearance.⁷⁰ However, the underlying mechanisms of p62-mediated clearance in this pathway have not been fully understood. Previous studies have indicated that the autophagic clearance was regulated by Ser403 phosphorylation of p62, a step promoted by casein kinase 2 or TANK-binding kinase 1.^{71,72} Ro et al identified Unc-51-like protein kinase 1 as a novel p62 ser403 kinase, while Sertrin2 is a promoter of Ser403 phosphorylation.⁷³ Recently, multiple phosphorylation sites of p62 in ubiquitin association domains have been recognized,⁷⁴ of which phosphorylation of Ser409 by Unc-51-like protein kinase 1 significantly increases the binding affinity of p62 to ubiquitin under proteotoxic conditions. Thus, the phosphorylated p62 linked with the damaged mitochondria by ubiquitin is recognized by the receptors on an autophagosome.

P62 also has an impact on the elimination of toxic proteins. Cigarette smoking-related COPD is known to induce an imbalance in protein homeostasis in the mitochondria, which initiates aggregation of ubiquitinated proteins,⁷⁵ which in turn promotes the accumulation of PINK1 and leads to mitophagy. Thus, autophagy is responsible for the elimination of these aggregative proteins. The targeting cargo of mitophagy to autophagosomes is recognized by a body of ubiquitin-binding autophagic adaptors (eg, p62/SQSTM1/sequestosome-1), which connect the ubiquitin system and the autophagic mechanism, promoting the binding of autophagic substrates and the small ubiquitin-like modifiers that belong to the autophagy-related 8/LC3 family located on the membrane of autophagosomes.⁷⁶ Furthermore, the cargo receptor for autophagic degradation, p62, has also been identified as a target gene for the transcription factor Nrf2 and creates a positive feedback loop for oxidative stress by activation of

antioxidant response.⁷⁷ Another study indicated that Nrf2 knockout in the *Staphylococcus aureus* sepsis model induced dysregulated autophagy of the alveolar cells, which led to accumulation of p62 and increased colocalization of LC3 to mitochondria.⁷⁸ Thus, Nrf2-dependent mitophagy or p62-targeted phosphorylation may provide a potential novel drug target for oxidative stress-related lung disease. Additionally, recent studies have indicated that mitophagic clearance also aggravates the pathogenesis of COPD. Significant accumulation of polyubiquitinated proteins and p62 was detected in the lungs when exposed to cigarette smoke extract, which accelerated lung aging and COPD-emphysema exacerbations.⁷⁹ P62 as an impaired autophagy marker showed an increased level in aggresome bodies in the cells exposed to cigarette smoke extract. Recently, PINK-induced mitochondrial instability was found to be correlated with Fbxo15, an ubiquitin E3 ligase component.⁸⁰ The interaction between PINK1 and Fbxo15 triggers polyubiquitination and proteasomal elimination of cardiolipin synthase, thus impairing the mitochondrial membrane.⁸⁰ Mitophagy also occurred in emphysema and airway disruption, during which process the Akt ubiquitin E3 ligase mitochondrial E3 ubiquitin protein ligase 1 was identified as a novel mediator associated with cigarette smoking-induced pulmonary endothelial cell death and mitochondrial dysfunction.⁸¹ The level of mitochondrial E3 ubiquitin protein ligase 1 was noticeably elevated after exposure to cigarette smoke, potentially contributing to endothelial cell death and dysfunction in the lungs of smokers. Thus, we can presume that the alternative PINK targets or ubiquitin E3 ligase may have a potential application in the therapeutic treatment in COPD, and further investigations are necessary to explore the effects of mitophagy in the pathogenesis of COPD.

Conclusion

Oxidative stress is involved in the pathogenesis and progression of COPD and is also of great importance in the initiation of inflammation. It contributes the most to COPD by disturbing the antioxidant system and the balance of oxidant/antioxidant within the cells, accompanied by an increased risk of comorbid diseases or inflammation. As one of the main producers of ROS, mitochondria undergo a series of changes in morphology. These alterations, such as mitochondrial fission/fusion or mitophagy, are stress reactions in response to excessive oxidation, which provides a train of thought of alleviating partial injuries of cells by targeting certain molecules. Therapies targeting enhancement of antioxidants' ability seem to be able to reduce COPD exacerbations by modulating the oxidative stress. However, untargeted antioxidants

such as vitamin E and NAC lack beneficial effects sometimes or may even worsen the disease. Mitochondria-targeted antioxidants such as Mito-TEMPO have been validated for their effective role in restoring impaired mitophagy and in delaying cellular senescence in Parkin-overexpressing cells. Thus, further research that focuses on mitochondria should be carried out because it may provide important information on the potential therapeutic strategies for the treatment of COPD patients.

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Disclosure

The authors report no conflicts of interest in this work.

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