Mitochondrial damage-associated molecular patterns in chronic obstructive pulmonary disease: Pathogenetic mechanism and therapeutic target

Yongchun Shen[#], Lei Chen[#], Jun Chen, Jiangyue Qin, Tao Wang, Fuqiang Wen

Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China, Chengdu 610041, Sichuan Province, China

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a common inflammatory airway disease characterized by enhanced inflammation. Recent studies suggest that mitochondrial damage-associated molecular patterns (DAMPs) may play an important role in the regulation of inflammation and are involved in a serial of inflammatory diseases, and they may also be involved in COPD. This review highlights the potential role of mitochondrial DAMPs during COPD pathogenesis and discusses the therapeutic potential of targeting mitochondrial DAMPs and their related signaling pathways and receptors for COPD. Research progress on mitochondrial DAMPs may enhance our understanding of COPD inflammation and provide novel therapeutic targets.

Key words: chronic obstructive pulmonary disease, mitochondrial damage-associated molecular patterns, inflammation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease that features airway limitation and persistent respiratory symptoms. COPD is a leading cause of morbidity and mortality worldwide and brings heavy economic and social burdens that are both substantial and increasing.[1] Data from a large cross-sectional study revealed that the overall prevalence of spirometry-defined COPD was 8.6%, accounting for 99.9 million people with COPD in China alone.[2] COPD is one of the largest causes of mortality in most countries; in 2011, COPD was the third leading cause of death in the USA,[3] and in 2017, COPD was the fourth leading cause of years of life lost in China.[4] These statistics underscore the clinical challenge of improving COPD management.

The pathogenesis of COPD is complicated and has not been fully explained. Chronic irritation such as cigarette smoke (CS)-induced inflammatory response of the airway is considered as one of the most important pathogenetic factors of COPD, as evidenced by enhanced inflammatory cells and inflammatory mediators that amplify inflammation and induce structural changes in the airway and lungs.[5,6] CS-induced persistent airway inflammation causes airway limitation, gas trapping, gas exchange abnormalities, airway mucus hypersecretion, and acute exacerbations.[5-8] Modulation of airway inflammation is still an important method to treat COPD.

Mitochondria are vital cellular organelles crucial for energy generation, maintenance of cellular metabolism, intracellular signaling, calcium homeostasis, and modulation of cell death programs.[9,10] Emerging studies suggest that mitochondrial dysfunction plays an important role in the initiation and progression of many human diseases. A growing body of evidence

[#]These authors contributed equally to this work.

Address for Correspondence:
Prof. Fuqiang Wen, MD, PhD, Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University and Division of Pulmonary Diseases, State Key Laboratory of Biotherapy of China, No 37, Guixuexiang, Chengdu 610041, Sichuan Province, China.
E-mail: wenfuqiang@scu.edu.cn

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2022-0019

Open Access. © 2023 The author(s), published by De Gruyter on behalf of Scholar Media Publishing. This work is licensed under the Creative Commons Attribution-NonCommercial-No-Derivatives 4.0 International License.

suggests that CS-induced mitochondrial dysfunction, including mitochondrial biological function disorder, formatting harmful substances, abnormal mitophagy, and mitochondria-dependent signaling pathway dysregulation, exists in the context of COPD; mitochondrial dysfunction may also play an important role in regulating inflammation, and thus has a potential role in COPD.[11-14] More and more researchers are investigating COPD pathogenesis and searching for novel therapeutic targets from a mitochondrial perspective.

Damage-associated molecular patterns (DAMPs) are intracellular molecules released into the extracellular space by cells under stress; they can bind to pattern recognition receptors (PRRs) and activate a series of inflammatory pathways that affect disease occurrence, development, and outcome.[15] Mitochondrial dysfunction under various stimuli including CS may seriously affect cell energy metabolism and cause the release of many mitochondrial components (named as mitochondrial DAMPs) into the cytosol or extracellular space; these go on to take part in apoptosis, necrosis, inflammation, and other pathophysiological processes.[9] Mitochondrial DAMPs contain mitochondrial DNA, mitochondrial transcription factor A (TFAM), adenosine triphosphate (ATP), succinate, heat shock protein 60 (HSP60), cytochrome c, *N*-formyl peptides (NFPs), and cardiolipin, which have been identified as important mediators of the innate immune response and implicated in infection, trauma, acute lung injury, sepsis, autoimmune disorders, ischemic heart disease, and cancer.[16-18] Mitochondrial DAMPs are hot research topics and may help to understand the pathogenesis of diseases and diagnose, stage, treat, and prognostically evaluate diseases. Growing studies suggest that CS exposure may cause mitochondrial damage and dysfunction, and generation of mitochondrial DAMPs, and plays a role in COPD. This review highlights the role of the different mitochondrial DAMPs and related signal pathways in COPD and discusses their therapeutic potential.

CS AND MITOCHONDRIAL DAMPS

CS is considered as one of the most important risk factors of COPD, and growing studies suggest that CS is associated with the damage of mitochondrial DAMPs through several mechanisms. First, a previous study found that long-term exposure to CS extract (CSE) causes significant changes in the mitochondrial structure in BEAS-2B cells, including branching fragmentation and reduction in cristae quantity, which may be through the regulation of specific fission/fusion proteins (Fis1, Mfn1, Mfn2, Drp1, and Opa1), oxidative phosphorylation proteins (complex II, III, and V), oxidative stress, and inflammatory response. Similar findings were identified in primary bronchial epithelial cells from patients with COPD. These results suggest CS can impair the mitochondrial structure and cause the damage of mitochondria.[19] Second, CS exposure can cause mitochondrial dysfunction. Even mild and nontoxic doses of CSE could induce mitochondrial hyperfusion in murine lung epithelial and primary mouse alveolar epithelial cells, which may contribute to COPD pathogenesis.[20] CS also blocks the mitochondrial respiratory chain, with decreases in mitochondrial membrane potential, mitochondrial oxygen consumption, and production of ATP, and causes mitochondrial dysfunction.[21] Third, the injured or dysfunctional mitochondria are normally cleared from the cell by mitophagy, while growing evidence suggests that CS exposure could impair mitophagy and reduce the ability of eliminating damaged mitochondria. The accumulation of damaged or dysfunctional mitochondria may cause subsequent inflammation, oxidative stress, is associated with many chronic lung diseases including COPD.[22-24] All these studies suggest that CS can damage mitochondria and may contribute to mitochondrial DAMPs' generation.

More and more direct evidence revealed that CS is associated with the generation of mitochondrial DAMPs. Smokers had 5.6 times the level of mitochondrial DNA damage and 2.6 times the damage at a nuclear locus compared to nonsmokers in the bronchoalveolar lavage tissues.[25] CS exposure significantly affects mitochondrial function, characterized by decreased intracellular ATP levels and increased mitochondrial DNA in human neutrophils,[26] suggesting that CS may induce mitochondrial DAMPs' release from necrotic neutrophils to trigger proinflammatory mediator release, followed by enhanced inflammation. Acrolein is a major component of CS and can cause various lung diseases including asthma, COPD, and lung cancer. It can induce mitochondrial DNA damage and alter mtDNA copy number in human lung epithelial cells and fibroblasts, as well as alter cytochrome c release in A549 human lung cells.[27,28] The collective available evidence supports the hypothesis that when mitochondria are stressed or functionally impaired by CS, they can release a variety of mitochondrial DAMPs that drive inflammatory responses and take part in COPD pathogenesis.

MITOCHONDRIAL DAMPS AND COPD

Mitochondrial DNA

Mitochondrial DNA is released into the cytosol or circulation from damaged mitochondria and serves as DAMPs that regulate the immune system and inflammation.[29,30] Many studies have reported that mitochondrial DNA is involved in numerous diseases

like acute lung injury, sepsis, trauma, pulmonary embolism, liver failure, cancer, myocardial infarction, rheumatoid arthritis, and neurological disorders.[17,29,30] Mitochondrial DNA is considered as an important regulator of inflammatory diseases.

Several clinical studies have described a role of mitochondrial DNA in COPD. Zhang *et al.* found that patients with mild or moderate COPD had higher plasma mitochondrial DNA levels compared to ever smokers without COPD, while participants with severe COPD had lower plasma mitochondrial DNA levels compared to those with mild or moderate COPD. Clinical data revealed that plasma mitochondrial DNA levels may be associated with baseline COPD status, but not future changes in clinical COPD measures.[31] The same group reported that urine mitochondrial DNA levels may help identify distinct clinical phenotypes and underlying pathobiological differences in males versus females with COPD.[32] Mitochondrial DNA/nuclear DNA levels in exhaled breath condensate are increased in COPD patients compared to healthy subjects.[33] Overall, these findings suggest a role for mitochondrial dysfunction in severe COPD and suggest a need for future longitudinal investigations to measure mitochondrial DNA and examine their clinical significance.

The direct mechanism by which mitochondrial DNA affects COPD is still unclear. It is well recognized that mitochondrial DNA can trigger an inflammatory response through interaction with Toll-like receptor 9 (TLR9), inflammasomes, and cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING).[14,17] TLR9 is the first discovered receptor that can recognize unmethylated CpG DNA, typical of bacterial DNA, viral DNA, and mitochondrial DNA. Studies reported that unmethylated CpG sequences present in mitochondrial DNA molecules can activate TLR9 through a sequence-specific binding to the N-term of the C-shaped, leucine-rich repeat region of TLR9. Then, the cytosolic domain of TLR9 induces the activation of MyD88 pathway, mitogen-activated protein kinase (MAPK), and NF-$\varkappa$B signaling pathway, leading to the transcription of inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and adhesion molecules.[34,35] An animal study reported that intratracheal administration of mitochondrial DNA could induce lung inflammatory response in mice, which was through the interaction with TLR9 and related MAPK signaling transduction pathway.[36] CS exposure enhanced TLR9 expression in the lung of a mouse emphysema model, which regulated CS-mediated immune cell recruitment to the lung, apoptosis, and inflammatory mediator expression.[37] CSE also upregulated TLR9 expression in human neutrophils, and since TLR9 mediates CSE-induced release of CXCL8, it may contribute to neutrophil accumulation and inflammation within the airways of smokers.[38] CS may increase the release of mitochondrial DNA and then interact with TLR9, contributing to airway inflammation. These findings suggest that TLR9 is an important therapeutic target of COPD.

Inflammasomes are targets of mitochondrial DNA and play an important role in regulating inflammation and COPD; NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) are the most important inflammasome components.[39] Mitochondrial DNA can directly induce NLRP3 inflammasome activation and has been reported in various studies.[40-42] Lipopolysaccharide (LPS) and ATP stimulus promoted the cytosolic translocation of mitochondrial DNA, and the cytosolic accumulation of mitochondrial DNA was mediated by NLPR3 inflammasome and mitochondrial reactive oxygen species (ROS) in macrophages. The cytosolic mitochondrial DNA contributed to the secretion of inflammatory cytokines IL-1β and IL-18, which take part in the inflammatory response.[43] Intratracheal administration of extracellular mtDNA induces NLRP3 inflammasome activation, acute lung inflammation, and injury through TLR9, p38 MAPK, and NF-$\varkappa$B pathways.[44] NLRP3 mRNA was upregulated in the lung tissue samples of stable COPD patients compared to controls,[45] but this association was not confirmed in bronchial mucosa examined with immunohistochemistry.[46] NLRP3 inflammasomes were upregulated and activated in an *in vitro* model of COPD exacerbation,[47] and clinical studies confirmed that systemic and local airway NLRP3 inflammasome activation is associated with acute exacerbation, suggesting that it might be a predictive factor of outcomes in COPD patients.[48] In mice and L-132 alveolar epithelial cells, CS induced mitochondrial dysfunction, which activated the NLRP3 inflammasome to mediate IL-1β and IL-18 release and a subsequent inflammatory response.[49] NLRP3 knockout protected mice from CS-induced airway inflammation, indicating that NLRP3 blockade might be a therapeutic strategy for COPD.[50]

Mitochondrial DNA could also be recognized by another DNA-sensing pathway of the innate immune system, the cGAS–STING axis that triggers a type I interferon response, which is important for COPD development.[14,17,34] As a DNA sensor, cGAS binds to mtDNA and promotes the recruitment of STING protein, an endoplasmic reticulum–anchored cytosolic protein which triggers phosphorylation of the transcription factor IRF-3. The activated IRF-3 mediates interferon (IFN) response and results in mitochondrial DNA-induced inflammatory responses.[51] The intracellular mitochondrial DNA can also induce the STING-mediated IFN response.[52,53] Exposure to CS triggers the DNA sensor cGAS and

STING, driving type I IFN-dependent lung inflammation, which is attenuated in cGAS, STING-deficient mice.[54] Another study reported that CS or CSE exposure alone inhibited STING expression, indicating that STING may play a protective role in preventing COPD progression.[55] Blocking the interaction between mitochondrial DNA and related PPRs may be a novel therapeutic method for COPD.

Mitochondrial transcription factor A

TFAM is a nucleus-encoded protein that regulates the transcription and replication of mitochondrial DNA, and growing evidence suggests that it plays a role in the regulation of inflammation and oxidative stress.[56] However, few studies have investigated the potential role of TFAM in COPD.

Peng *et al.* reported that TFAM mRNA and protein expression were downregulated in lung tissues from COPD patients with squamous cell lung cancer. TFAM protein levels are related to the lung function of patients and pulmonary vascular endothelial cell apoptosis, and TFAM promoter methylation degree was increased in patients with COPD compared to non-COPD patients.[57] The same group found that TFAM mRNA and protein expression were downregulated in CSE-treated human umbilical vein endothelial cells due to TFAM promoter hypermethylation; their findings may provide a novel strategy for COPD by developing demethylation agents targeting TFAM.[58] Further mechanistic experiments revealed that TFAM promotor methylation is involved in Notch 1 and ERK-mediated CS-induced endothelial apoptosis.[59] Another study found that TFAM regulated renal inflammation through the modulation of STING pathway.[60] Transcriptome analysis revealed that TFAM overexpression caused significant differentially expressed genes in human lung epithelial cells. TFAM-repressed genes were mainly enriched in type I IFN- and INF-γ–mediated signaling pathways, cytokine-mediated signaling pathway, and viral response pathways.[61] These results suggest that TFAM may take part in the regulation of inflammation in COPD through various pathways. TFAM may be an important therapeutic target in COPD.

Adenosine triphosphate

ATP plays a critical role in cellular energetics and metabolism. Under physiologic and pathophysiologic conditions, ATP is released from cells, and induces a series of immune responses and participates in the regulation of a variety of cellular functions. Many studies have investigated the role of ATP in COPD.[62,63]

COPD is characterized by persistent upregulation of extracellular ATP in the airways, as evidenced by increased ATP concentrations in bronchoalveolar lavage fluid (BALF) in both smokers and ex-smokers with COPD. Increased BALF ATP concentrations are negatively and positively correlated with lung function and BALF neutrophil counts, respectively, in patients with COPD. ATP induces stronger chemotaxis and elastase release in blood neutrophils and stimulates increased secretion of proinflammatory and tissue-degrading mediators in airway macrophages from patients with COPD.[64] A recent study reported elevated plasma extracellular ATP concentration in COPD patients compared to controls, and increased levels were related to airway limitation severity (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2–4), symptom burden, and history of exacerbations.[65] Extracellular ATP may become a diagnostic and prognostic biomarker of COPD, as it seems helpful for evaluating patients' condition, quality of life, and disease progression.

Compared to healthy subjects, ATP induced more dyspnea, cough, and throat irritation in smokers and patients with COPD, suggesting a potential role of ATP in COPD.[66] The effects of ATP are mainly mediated through its interactions with ATP-recognizing receptors like P2Y2R or P2X(7) R. Cicko *et al.* reported elevated endogenous pulmonary ATP levels in a smoke-induced mouse model, but ATP neutralization or nonspecific P2R blockade markedly reduced lung inflammation and emphysema, while P2Y(2) R-deficient animals had reduced pulmonary inflammation following acute smoke exposure.[67] Studies from the same group revealed that selective intrapulmonary inhibition of P2X(7)R attenuated CS-induced lung inflammation and prevented the development of emphysema, while P2X(7)R knockout also protected mice from lung inflammation induced by acute CS exposure.[68] Airway mucus hypersecretion is an important feature of COPD, and *in vitro* studies showed that dsRNA induces the release of ATP that regulates the expression and release of MUC5AC, mainly via P2Y(2)R in an autocrine manner.[69] Another study found that ATP-mediated MUC5AC production in NCI-H292 cells was almost equally blunted by nonspecific and specific antagonists of the purinergic receptor P2X(7)R, which mediated NLRP3 inflammasome activation by ATP.[70] The various ATP signaling pathways in airway inflammation and airway mucus hypersecretion are attractive targets for novel drug candidates that would improve COPD management.

Succinate

Succinate is a metabolic intermediate generated in mitochondria via the tricarboxylic acid cycle that plays an essential role in maintaining mitochondrial function. A recent study suggests that in addition to its crucial role in ATP production, succinate can also act as a DAMP and induce inflammation.[71] Another group reported that succinate may act as an inflammatory signal to regulate

hypoxia-inducible factor-1α (HIF-1α) signaling and promote macrophage-mediated inflammation.[72] However, a recent publication provided evidence that succinate can suppress secretion of the inflammatory mediators IL-6, TNF, and nitric oxide (NO), as well as inhibit IL-1β mRNA expression in inflammatory macrophages.[73] How succinate elicits anti-inflammatory or proinflammatory responses remains a debatable topic.

Evidence for a role of succinate in COPD is still limited. CS altered the metabotype of basal cells in airway epithelium, and succinate was significantly decreased in basal cells from smokers.[74] *Pseudomonas aeruginosa* is typically associated with infection in patients with COPD. Using LPS as a surrogate for bacterial infection, mitochondria shunt succinate into the cytoplasm, which inhibits prolylhydroxylase activity and enables stabilization of HIF-1α, which promotes IL-1β production initiating a proinflammatory response.[72,75] Thus, the immunometabolite succinate is released during airway infection and contributes to potential airway inflammation caused by infection in COPD. A clinical study based on plasma metabolomics was conducted to investigate the differential expression of metabolites between two COPD phenotypes: emphysema severity ≥grade 2 without bronchial wall thickening and emphysema severity ≥grade 2 and bronchial wall thickening ≥grade 1. Plasma succinate levels were higher in the latter group, suggesting it as a potential biomarker role in COPD.[76] However, the understanding of succinate in COPD inflammation remains unclear, so further studies should be performed to investigate its role in disease pathogenesis.

Heat shock protein 60

HSP60 is a major ATP-dependent mitochondrial chaperone, and previous studies have revealed that it serves an important role in the pathologies of complex conditions such as cancer, heart diseases, neurodegenerative disorders, and multiple inflammatory diseases.[77,78]

In 2011, Cappello *et al.* reported increased HSP60 immunohistochemistry in the bronchial epithelium of subjects with severe/very severe COPD compared to control nonsmokers, and these values positively correlated with neutrophils.[79] A recent study reported higher intracellular levels of HSP60 in COPD cases, and levels were increased in the GOLD1 group compared to the other severity groups, albeit without significance.[80] However, another group found no difference in HSP60 expression between subjects with COPD and controls.[81]

A few studies have elucidated a potential role of HSP60 in regulating inflammation in COPD. HSP60 exerted proinflammatory properties in bronchial epithelial cells by upregulating IL-8 and downregulating IL-10 at mRNA and protein levels.[82] Oxidative stress is a hallmark of COPD mucosa induced by H_2O_2 and could increase HSP60 levels through the regulation of NF-κB in bronchial epithelial cells (16HBE), and HSP60 also has a role in maintaining inflammation.[79] CS induced the expression of HSP60 in the COPD mouse model, which accelerated the TLR4–MyD88–NF-κB signaling pathway and the NLRP3 inflammasome and played a role in promoting COPD.[83] *C. pneumonia* is a common cause of bacterial pneumonia and has been implicated in the pathogenesis of COPD. As one of the pathogenic components of *C. pneumonia*, HSP60 causes significant lung inflammatory injuries.[84] The results of these studies should prompt further work on more complex *ex vivo* or *in vivo* models to further elucidate the role of HSP60 in COPD pathogenesis. These could be used to test efficacious anti-inflammatory therapies for COPD centered on HSP60.

Cytochrome c

Cytochrome c is released from the inner mitochondrial membrane into the cytoplasm under various stimuli and plays an important role in the regulation of apoptosis and inflammation.[85] The potential association between cytochrome c and COPD has been investigated in several studies.

Clinical studies revealed that cytochrome c releases are abnormal in the skeletal and respiratory muscles of patients with moderate COPD, indicating that there is a systemic effect of the disease.[86] Zhang *et al.* reported elevated plasma levels of cytochrome c in patients with COPD compared to controls, and was associated inversely with forced expiratory volume (FEV)1% predicted and FEV in 1 s/forced vital capacity and positively with COPD Assessment Test score, but no correlations were found between cytochrome c levels and inflammatory biomarkers, pack-years, or body mass index.[87] Overall, the results suggest that cytochrome c may be a useful clinical biomarker of COPD.

CS exposure has a significant effect on cytochrome c release. A previous study reported that CSE injection increased the expression of cytosolic cytochrome c in mice.[88] CSE also caused a significant reduction in mitochondrial cytochrome c and an increase in cytosolic cytochrome c in the A549 airway epithelial cell line.[89] CSE-induced toxicity in the lung tissue is a result of disruption of the mitochondrial respiratory chain that leads to ROS formation, lipid peroxidation, and cytochrome c expulsion, all of which contribute to apoptosis signaling and cell loss.[90] Collectively, these findings suggest that CS-induced abnormal cytochrome c release is a systemic mechanism occurring early during the course of the COPD that contributes to disease pathogenesis.

Reducing cytochrome c release may provide a protective effect against CS-induced airway inflammation and mucus hypersecretion. Our team's studies confirmed these findings, and CS exposure significantly increased the amount of cytochrome c released into the cytosol in the lungs of mice. Notably, treatment with mitochondria-targeted mitoquinone and mitochondria-targeting antioxidant SS-31 significantly reduced cytochrome c release and attenuated CS-induced thickening of the airway epithelium, peribronchial inflammatory cell infiltration, goblet cell hyperplasia, and Muc5ac staining.[91,92] Targeting cytochrome c may, therefore, be a novel therapeutic opinion for COPD.

NFPs and related receptors

NFPs are in the mitochondrial membrane and can be released into the extracellular milieu after cell membrane rupture or around dying cells. NFPs trigger similar sterile immune responses and function to attract neutrophils to the sites of inflammation where they work in concert with TFAM to activate inflammatory cells, contributing to various conditions including systemic inflammatory response syndrome, sepsis, and acute respiratory distress syndrome.[93-95] Our team found that NFPs released upon intratracheal challenge caused neutrophil accumulation in the alveolar space with elevated BALF levels of mouse keratinocyte chemoattractant, IL-1β, and NO, all of which induce inflammatory lung injury in mice.[96] After stimulation with *N*-formyl-l-methionyl-l-leucyl-l-phenylalanine (fMLP), neutrophils isolated from peripheral blood of smokers and patients with COPD showed an increased response on oxidative burst, chemotaxis, and elastase release.[97] Mice treated with fMLP instillation developed emphysema changes, airway inflammation, and goblet cell metaplasia in the lung.[97,98] Wenceslau *et al.* found that NFPs induced concentration-dependent contractions in the trachea, bronchi, and bronchioles, while intratracheal challenge with NFPs increased neutrophil elastase expression in the lung and enhanced inducible NO synthase in all airway segments.[99] This evidence suggests a potential role of NFPs in obstructive and inflammatory lung diseases like COPD.

The action of NFP is mainly mediated through interaction with formyl peptide receptors (FPRs); these G protein-coupled receptors transduce chemotactic signals and mediate host defense as well as inflammatory responses.[100,101] Among the three human FPRs (FPR1, FPR2, and FPR3), FPR1 and FPR2 are drawing increasing attention.

Formyl peptide receptor 1

FPR1 is a member of the FPR family and potentially a key receptor within the inflammatory process.[102] NFPs bind to FPR1 on the neutrophil membrane, desensitizing FPR1 and other GPCRs via internalization of the receptors, followed by cell chemotaxis and the inflammatory process.[102,103] Our previous study confirmed that mitochondrial DAMPs activated FPR1 and exacerbated lung fluid imbalance in an experimental acute lung injury model.[104] Mitochondrial DAMPs from fractures also take part in pulmonary immune responses through the modulation of FPR1,[105] suggesting their potential roles in inflammatory lung diseases. FPR1 knockout confers protection from CS-induced lung emphysema in mice, while administration of the FPR1 antagonist cyclosporine H to wild-type mice attenuated lung inflammatory responses evoked by CS.[106] Our study also confirmed that FPR1 knockout attenuated several changes induced by CS exposure, including significant lung inflammatory changes, and a transcriptomic gene study showed that such effects may be mediated by immune-chemotaxis responses and inhibition of NF-κB activation.[107] Current findings suggest that airway inflammation persists even after smoking cessation, but the FPR1 antagonist cyclosporin H given after cessation led to a significant reduction of neutrophil migration in BALF compared to untreated mice exposed to CS for 4 months.[108] Less neutrophilic inflammation with FPR1 antagonists after cigarette cessation strongly suggested an important role of FPR1 signaling in modulating the inflammatory response after lung injury was already present. These findings may have clinical significance because current smokers and subjects with emphysema and COPD showed increased FPR1 expression, indicating that FPR1 modulation should be explored as a potential new therapy.

Formyl peptide receptor 2

FPR2 also plays an important role in inflammation regulation, and NFPs are well recognized as ligands of FRP2.[100,101,109] FPR2 expression on Th/Tc cells and serum annexin A1 (an endogenous FPR2 ligand) levels were both decreased in COPD patients compared to healthy nonsmokers, and FPR2 expression on neutrophils was also decreased in COPD patients with a frequent history of moderate exacerbation (≥2 events in the past 1 year).[110] The results suggest that defective FPR2 is associated with decreased M2a macrophage polarization and might be involved in the development of CS-induced inflammation and persistent airflow limitation in COPD.[110] Enhancing the expression and function of FRP2 may be a therapeutic target of COPD.

The endogenous FPR2 ligand resolvin-D1 has been shown to have therapeutic potential for CS-induced airway inflammation. Resolvin-D1 suppressed the production of proinflammatory mediators by primary human cells, and concurrent treatment of mice with resolvin-D1 and CS exposure significantly reduced neutrophilic lung inflammation, proinflammatory cytokine production, and

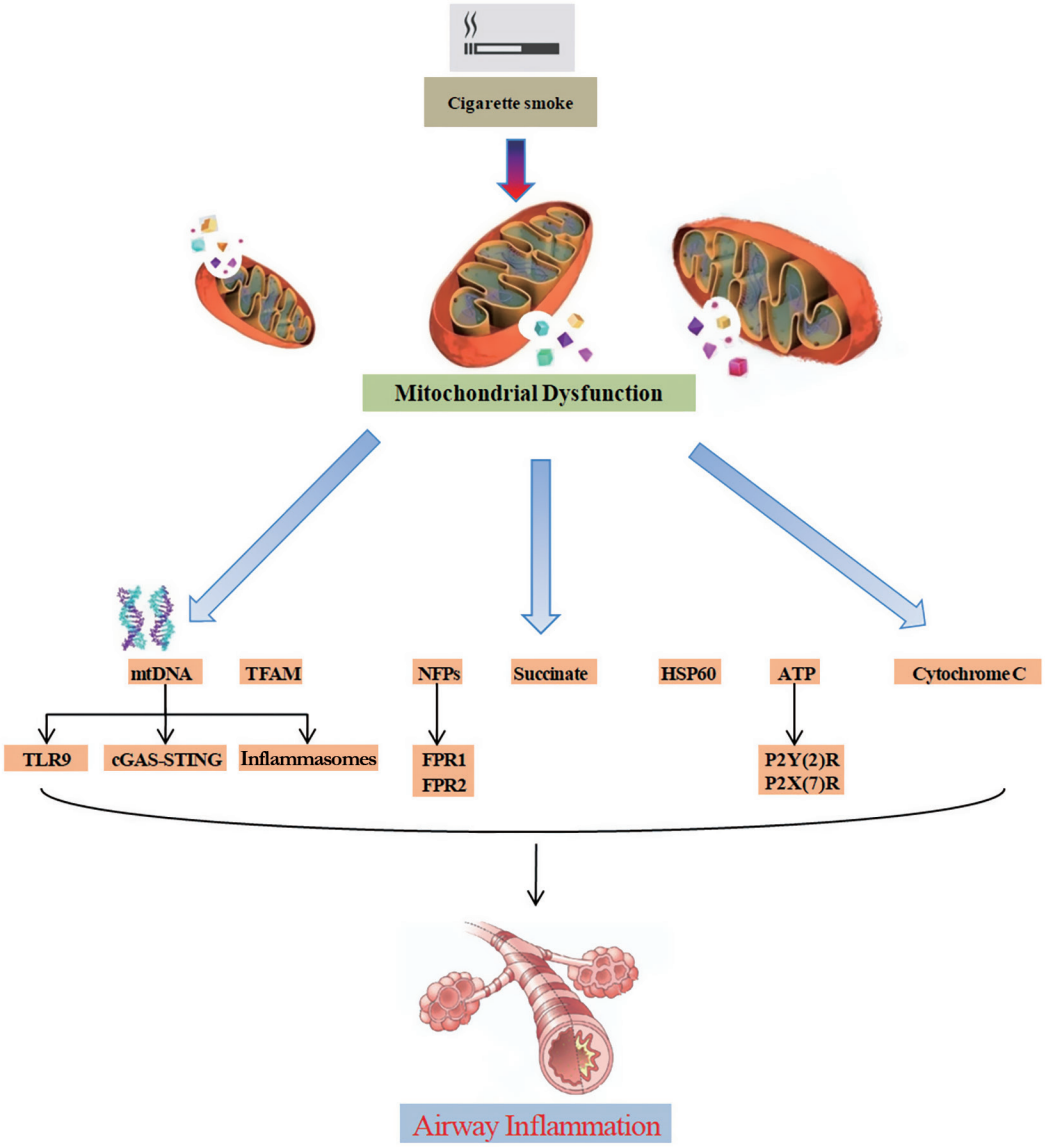

Figure 1: Overview of mitochondrial damage-associated molecular patterns in chronic obstructive pulmonary disease. ATP: adenosine triphosphate; cGAS: cyclic GMP–AMP synthase; FPR: formyl peptide receptor; HSP60: Heat shock protein 60; NFPs: N-formyl peptides; STING, stimulator of interferon genes; TFAM: mitochondrial transcription factor A; TLR9: Toll-like receptor 9.

anti-inflammatory cytokine upregulation.[111] In another animal study, resolvin-D1 significantly attenuated CS-induced lung destruction in emphysema models and reduced CS-induced inflammatory cell infiltration that causes the structural derangements that characterize emphysema.[112] The endogenous FPR2 ligand annexin A1 shows anti-inflammatory features and is also involved in COPD. The annexin A1 mimetic peptide Ac2-26 protected against leukocyte influx in BALF and reduced proinflammatory mediator levels in BALF in a rat model of COPD.[113] These studies suggest that resolvin-D1 and annexin A1 mimetic peptide have potent anti-inflammatory roles in cells or rodents exposed to CS, indicating that FPR2 modulation has strong potential as a novel therapeutic approach to COPD. The overview of mitochondrial DAMPs in COPD is shown in Figure 1.

PERSPECTIVES

Role of mitochondrial DAMPs as COPD biomarkers

The precise evaluation of COPD patients remains a clinical challenge, and there is an active search to find a novel and reliable biomarker of COPD. Endostatin, CXCL5, and syndecan-1 have been reported as possible COPD biomarkers, and the main associations between these markers are lung function and systemic inflammation.[113-115] Limited studies have discussed the potential role of mitochondrial DNA cytochrome c as a biomarker of COPD. However,

the role of mitochondrial DAMPs in COPD diagnosis, evaluation of lung function, prediction of exacerbation risk, mortality, airway and systemic inflammation, clinical phenotype, treatment response, and clinical prognosis has not been fully examined, and further studies should be performed to determine the role of mitochondrial DAMPs as a biomarker of COPD.

COPD treatment based on mitochondrial DAMPs and related signal pathways

Therapeutically targeting mitochondrial DAMPs and their signaling pathways is a promising COPD treatment avenue. There are several different approaches, some of which are as follows: to prevent the leak of proinflammatory mitochondrial DAMPs into the cytosol or the extracellular space, remove existing mitochondrial DAMPs to prevent mitochondrial dysfunction, and protect the mitochondria from CS insults and maintain the normal organelle function. Mitochondria-targeted mitoquinone, the mitochondria-targeting antioxidant SS-31, and other mitochondria-targeted agents that can ameliorate mitochondrial dysfunction and improve the eliminating of damaged mitochondria may be promising drugs for COPD.

Blocking the receptors that interact with mitochondrial DAMPs has also shown great potential for COPD therapy. Based on previous studies, modulation of TLR9, NLRP3 inflammasomes, STING, FPR1, and FPR2 shows potential therapeutic effects for COPD. Even so, we have not searched related therapeutic clinical trials based on mitochondrial DAMPs and related receptors for COPD. There is still a long road from basic research to clinical use, and further work should be carried out to investigate the effects of novel therapeutic agents that modulate mitochondrial DAMPs and related signal pathways.

CONCLUSIONS

Numerous studies suggest that the risk factors of COPD, like CS, can cause mitochondrial injury and the release of mitochondrial DAMPs, which combined with their receptors cause inflammation and contribute to COPD pathogenesis through a series of mechanisms. Further work should be performed to investigate the detailed mechanism of mitochondrial DAMPs in COPD and develop novel drugs for COPD based on mitochondrial DAMPs and related signaling pathways.

Conflicts of Interest

The authors declare no conflicts of interest. The funders had no roles in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Source of Funding

This work was supported by the National Natural Science Foundation of China (31871157, 81830001, and 82170046), 1•3•5 Project for Disciplines of Excellence, West China Hospital of Sichuan University (ZYGD18006, ZYJC18012) and Sichuan Key Research and Development Program (2020YFS0147).

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease (2021 Report) Available at: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Accessed October 22, 2021.
2. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, *et al.* Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet 2018;391:1706-17.
3. Hoyert DL, Xu JQ. Deaths: preliminary data for 2011. Natl Vital Stat Rep 2011;61:1-65.
4. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, *et al.* Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;394:1145-58.
5. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2016;138:16-27.
6. Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. Clin Chest Med 2014;35:71-86.
7. Hikichi M, Mizumura K, Maruoka S, Gon Y. Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. J Thorac Dis 2019;11:S2129-40.
8. Tian PW, Wen FQ. Clinical significance of airway mucus hypersecretion in chronic obstructive pulmonary disease. J Transl Int Med 2015;3:89-92.
9. Dela Cruz CS, Kang MJ. Mitochondrial dysfunction and damage associated molecular patterns (DAMPs) in chronic inflammatory diseases. Mitochondrion 2018;41:37-44.
10. Wang P, Zhang N, Wu B, Wu S, Zhang Y, Sun Y. The Role of Mitochondria in Vascular Calcification. J Transl Int Med 2020;8:80-90.
11. Ryter SW, Rosas IO, Owen CA, Martinez FJ, Choi ME, Lee CG, *et al.* Mitochondrial Dysfunction as a Pathogenic Mediator of Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc 2018;15:S266-72.
12. Prakash YS, Pabelick CM, Sieck GC. Mitochondrial Dysfunction in Airway Disease. Chest 2017;152:618-26.
13. Kang MJ, Shadel GS. A Mitochondrial Perspective of Chronic Obstructive Pulmonary Disease Pathogenesis. Tuberc Respir Dis (Seoul) 2016;79:207-13.
14. Zhou WC, Qu J, Xie SY, Sun Y, Yao HW. Mitochondrial Dysfunction in Chronic Respiratory Diseases: Implications for the Pathogenesis and Potential Therapeutics. Oxid Med Cell Longev 2021;2021:5188306.
15. Murao A, Aziz M, Wang H, Brenner M, Wang P. Release mechanisms of major DAMPs. Apoptosis 2021;26:152-62.
16. Li S, Hu Q, Huang J, Wu X, Ren J. Mitochondria-Derived Damage-Associated Molecular Patterns in Sepsis: From Bench to Bedside. Oxid Med Cell Longev 2019;2019:6914849.
17. Grazioli S, Pugin J. Mitochondrial Damage-Associated Molecular Patterns: From Inflammatory Signaling to Human Diseases. Front Immunol 2018;9:832.

18. Nakahira K, Hisata S, Choi AM. The Roles of Mitochondrial Damage-Associated Molecular Patterns in Diseases. Antioxid Redox Signal 2015; 23:1329-50.
19. Hoffmann RF, Zarrintan S, Brandenburg SM, Kol A, de Bruin HG, Jafari S, *et al.* Prolonged cigarette smoke exposure alters mitochondrial structure and function in airway epithelial cells. Respir Res 2013;14:97.
20. Ballweg K, Mutze K, Königshoff M, Eickelberg O, Meiners S. Cigarette smoke extract affects mitochondrial function in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 2014;307:L895-907.
21. van der Toorn M, Slebos DJ, de Bruin HG, Leuvenink HG, Bakker SJ, Gans RO, *et al.* Cigarette smoke-induced blockade of the mitochondrial respiratory chain switches lung epithelial cell apoptosis into necrosis. Am J Physiol Lung Cell Mol Physiol 2007;292:L1211-8.
22. Liu JY, Zhang MY, Qu YQ. The Underlying Role of Mitophagy in Different Regulatory Mechanisms of Chronic Obstructive Pulmonary Disease. Int J Chron Obstruct Pulmon Dis 2020;15:2167-77.
23. Ahmad T, Sundar IK, Lerner CA, Gerloff J, Tormos AM, Yao H, *et al.* Impaired mitophagy leads to cigarette smoke stress-induced cellular senescence: implications for chronic obstructive pulmonary disease. FASEB J 2015;29:2912-29.
24. Jiang S, Sun J, Mohammadtursun N, Hu Z, Li Q, Zhao Z, *et al.* Dual role of autophagy/mitophagy in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2019;56:116-25.
25. Ballinger SW, Bouder TG, Davis GS, Judice SA, Nicklas JA, Albertini RJ. Mitochondrial genome damage associated with cigarette smoking. Cancer Res 1996;56:5692-7.
26. Heijink IH, Pouwels SD, Leijendekker C, de Bruin HG, Zijlstra GJ, van der Vaart H, *et al.* Cigarette smoke-induced damage-associated molecular pattern release from necrotic neutrophils triggers proinflammatory mediator release. Am J Respir Cell Mol Biol 2015;52:554-562.
27. Wang HT, Lin JH, Yang CH, Haung CH, Weng CW, Maan-Yuh Lin A, *et al.* Acrolein induces mtDNA damages, mitochondrial fission and mitophagy in human lung cells. Oncotarget 2017;8:70406-70421.
28. Roy J, Pallepati P, Bettaieb A, Tanel A, Averill-Bates DA. Acrolein induces a cellular stress response and triggers mitochondrial apoptosis in A549 cells. Chem Biol Interact 2009;181:154-67.
29. Das P, Chakrabarti O. Mitochondrial DNA in innate immune responses against infectious diseases. Biochem Soc Trans 2020;48:2823-2838.
30. Riley JS, Tait SW. Mitochondrial DNA in inflammation and immunity. EMBO Rep 2020;21:e49799.
31. Zhang WZ, Hoffman KL, Schiffer KT, Oromendia C, Rice MC, Barjaktarevic I, *et al.* Association of plasma mitochondrial DNA with COPD severity and progression in the SPIROMICS cohort. Respir Res 2021;22:126.
32. Zhang WZ, Rice MC, Hoffman KL, Oromendia C, Barjaktarevic IZ, Wells JM, *et al.* Association of urine mitochondrial DNA with clinical measures of COPD in the SPIROMICS cohort. JCI Insight 2020;5:e133984.
33. Carpagnano GE, Lacedonia D, Carone M, Soccio P, Cotugno G, Palmiotti GA, *et al.* Study of mitochondrial DNA alteration in the exhaled breath condensate of patients affected by obstructive lung diseases. J Breath Res 2016;10:026005.
34. De Gaetano A, Solodka K, Zanini G, Selleri V, Mattioli AV, Nasi M, *et al.* Molecular Mechanisms of mtDNA-Mediated Inflammation. Cells 2021; 10:2898.
35. Ohto U, Shibata T, Tanji H, Ishida H, Krayukhina E, Uchiyama S, *et al.* Structural basis of CpG and inhibitory DNA recognition by Toll-like receptor 9. Nature 2015;520:702-5.
36. Gu X, Wu G, Yao Y, Zeng J, Shi D, Lv T, *et al.* Intratracheal administration of mitochondrial DNA directly provokes lung inflammation through the TLR9-p38 MAPK pathway. Free Radic Biol Med 2015;83:149-58.
37. Foronjy RF, Salathe MA, Dabo AJ, Baumlin N, Cummins N, Eden E, *et al.* TLR9 expression is required for the development of cigarette smoke-induced emphysema in mice. Am J Physiol Lung Cell Mol Physiol 2016; 311:L154-66.
38. Mortaz E, Adcock IM, Ito K, Kraneveld AD, Nijkamp FP, Folkerts G. Cigarette smoke induces CXCL8 production by human neutrophils via activation of TLR9 receptor. Eur Respir J 2010;36:1143-54.
39. Zhang J, Xu Q, Sun W, Zhou X, Fu D, Mao L. New Insights into the Role of NLRP3 Inflammasome in Pathogenesis and Treatment of Chronic Obstructive Pulmonary Disease. J Inflamm Res 2021;14:4155-68.
40. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature 2011;469:221-5.
41. Zhong Z, Liang S, Sanchez-Lopez E, He F, Shalapour S, Lin XJ, *et al.* New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. Nature 2018;560:198-203.
42. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, *et al.* Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 2012;36:401-14.
43. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, *et al.* Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011;12:222-30.
44. Wu G, Zhu Q, Zeng J, Gu X, Miao Y, Xu W, *et al.* Extracellular mitochondrial DNA promote NLRP3 inflammasome activation and induce acute lung injury through TLR9 and NF-κB. J Thorac Dis 2019;11:4816-28.
45. Faner R, Sobradillo P, Noguera A, Gomez C, Cruz T, López-Giraldo A, *et al.* The inflammasome pathway in stable COPD and acute exacerbations. ERJ Open Res 2016;2:00002-2016.
46. Di Stefano A, Caramori G, Barczyk A, Vicari C, Brun P, Zanini A, *et al.* Innate immunity but not NLRP3 inflammasome activation correlates with severity of stable COPD. Thorax 2014;69:516-24.
47. Nachmias N, Langier S, Brzezinski RY, Siterman M, Stark M, Etkin S, *et al.* NLRP3 inflammasome activity is upregulated in an in-vitro model of COPD exacerbation. PLoS One 2019;14:e0214622.
48. Wang H, Lv C, Wang S, Ying H, Weng Y, Yu W. NLRP3 Inflammasome Involves in the Acute Exacerbation of Patients with Chronic Obstructive Pulmonary Disease. Inflammation 2018;41:1321-33.
49. Mahalanobish S, Dutta S, Saha S, Sil PC. Melatonin induced suppression of ER stress and mitochondrial dysfunction inhibited NLRP3 inflammasome activation in COPD mice. Food Chem Toxicol 2020; 144:111588.
50. Yang W, Ni H, Wang H, Gu H. NLRP3 inflammasome is essential for the development of chronic obstructive pulmonary disease. Int J Clin Exp Pathol 2015;8:13209-16.
51. Barber GN. STING-dependent cytosolic DNA sensing pathways. Barber GN. Trends Immunol 2014;35:88-9.
52. Rongvaux A, Jackson R, Harman CC, Li T, West AP, de Zoete MR, *et al.* Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. Cell 2014;159:1563-77.
53. White MJ, McArthur K, Metcalf D, Lane RM, Cambier JC, Herold MJ, *et al.* Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell 2014;159:1549-62.
54. Nascimento M, Gombault A, Lacerda-Queiroz N, Panek C, Savigny F, Sbeity M, *et al.* Self-DNA release and STING-dependent sensing drives inflammation to cigarette smoke in mice. Sci Rep 2019;9:14848.
55. Qin H, Huang G, Gao F, Huang B, Wang D, Hu X, *et al.* Diminished stimulator of interferon genes production with cigarette smoke-exposure contributes to weakened anti-adenovirus vectors response and destruction of lung in chronic obstructive pulmonary disease model. Exp Cell Res 2019;384:111545.
56. Kang D, Kim SH, Hamasaki N. Mitochondrial transcription factor A (TFAM): roles in maintenance of mtDNA and cellular functions. Mitochondrion 2007;7:39-44.
57. Peng H, Yang M, Chen ZY, Chen P, Guan CX, Xiang XD, *et al.* Expression and methylation of mitochondrial transcription factor a in chronic obstructive pulmonary disease patients with lung cancer. PLoS One 2013;8:e82739.
58. Peng H, Guo T, Chen Z, Zhang H, Cai S, Yang M, *et al.* Hypermethylation

of mitochondrial transcription factor A induced by cigarette smoke is associated with chronic obstructive pulmonary disease. Exp Lung Res 2019;45:101-11.
59. Zong D, Li J, Cai S, He S, Liu Q, Jiang J, *et al*. Notch1 regulates endothelial apoptosis via the ERK pathway in chronic obstructive pulmonary disease. Am J Physiol Cell Physiol 2018;315:C330-40.
60. Chung KW, Dhillon P, Huang S, Sheng X, Shrestha R, Qiu C, *et al*. Mitochondrial Damage and Activation of the STING Pathway Lead to Renal Inflammation and Fibrosis. Cell Metab 2019;30:784-99.e5.
61. Luo J, Liu H, Li DKJ, Song B, Zhang Y. Repression of the expression of proinflammatory genes by mitochondrial transcription factor A is linked to its alternative splicing regulation in human lung epithelial cells. BMC Immunol 2021;22:74.
62. Mortaz E, Folkerts G, Nijkamp FP, Henricks PA. ATP and the pathogenesis of COPD. Eur J Pharmacol 2010;638:1-4.
63. Pelleg A. Extracellular adenosine 5'-triphosphate in pulmonary disorders. Biochem Pharmacol 2021;187:114319.
64. Lommatzsch M, Cicko S, Müller T, Lucattelli M, Bratke K, Stoll P, *et al*. Extracellular adenosine triphosphate and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181:928-34.
65. Hlapčić I, Hulina-Tomašković A, Somborac-Bačura A, Rajković MG, Dugac AV, Popović-Grle S, *et al*. Extracellular adenosine triphosphate is associated with airflow limitation severity and symptoms burden in patients with chronic obstructive pulmonary disease. Sci Rep 2019; 9:15349.
66. Basoglu OK, Barnes PJ, Kharitonov SA, Pelleg A. Effects of Aerosolized Adenosine 5'-Triphosphate in Smokers and Patients With COPD. Chest 2015;148:430-5.
67. Cicko S, Lucattelli M, Müller T, Lommatzsch M, De Cunto G, Cardini S, *et al*. Purinergic receptor inhibition prevents the development of smoke-induced lung injury and emphysema. J Immunol 2010;185:688-97.
68. Lucattelli M, Cicko S, Müller T, Lommatzsch M, De Cunto G, Cardini S, *et al*. P2X7 receptor signaling in the pathogenesis of smoke-induced lung inflammation and emphysema. Am J Respir Cell Mol Biol 2011; 44:423-9.
69. Shishikura Y, Koarai A, Aizawa H, Yamaya M, Sugiura H, Watanabe M, *et al*. Extracellular ATP is involved in dsRNA-induced MUC5AC production via P2Y2R in human airway epithelium. Respir Res 2016;17:121.
70. Kim K, Kim HJ, Binas B, Kang JH, Chung IY. Inflammatory mediators ATP and S100A12 activate the NLRP3 inflammasome to induce MUC5AC production in airway epithelial cells. Biochem Biophys Res Commun 2018;503:657-64.
71. Mills E, O'Neill L. Succinate: A metabolic signal in inflammation. Trends Cell Biol 2013;24:313-20.
72. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, *et al*. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature 2013;496:238-42.
73. Harber KJ, de Goede KE, Verberk SGS, Meinster E, de Vries HE, van Weeghel M, *et al*. Succinate Is an Inflammation-Induced Immunoregulatory Metabolite in Macrophages. Metabolites 2020;10:372.
74. Deeb RS, Walters MS, Strulovici-Barel Y, Chen Q, Gross SS, Crystal RG. Smoking-Associated Disordering of the Airway Basal Stem/Progenitor Cell Metabotype. Am J Respir Cell Mol Biol 2016;54:231-40.
75. Riquelme SA, Wong Fok Lung T, Prince A. Pulmonary Pathogens Adapt to Immune Signaling Metabolites in the Airway. Front Immunol 2020; 11:385.
76. Wang C, Li JX, Tang D, Zhang JQ, Fang LZ, Fu WP, *et al*. Metabolic changes of different high-resolution computed tomography phenotypes of COPD after budesonide–formoterol treatment. Int J Chron Obstruct Pulmon Dis 2017;12:3511-21.
77. Caruso Bavisotto C, Alberti G, Vitale AM, Paladino L, Campanella C, Rappa F, *et al*. Hsp60 Post-translational Modifications: Functional and Pathological Consequences. Front Mol Biosci 2020;7:95.
78. Khwaja B, Thankam FG, Agrawal DK. Mitochondrial DAMPs and altered mitochondrial dynamics in OxLDL burden in atherosclerosis. Mol Cell Biochem 2021;476:1915-28.
79. Cappello F, Caramori G, Campanella C, Vicari C, Gnemmi I, Zanini A, *et al*. Convergent sets of data from *in vivo* and *in vitro* methods point to an active role of Hsp60 in chronic obstructive pulmonary disease pathogenesis. PLoS One 2011;6:e28200.
80. Ambrocio-Ortiz E, Pérez-Rubio G, Ramírez-Venegas A, Hernández-Zenteno R, Del Angel-Pablo AD, Pérez-Rodríguez ME, *et al*. Effect of SNPs in HSP Family Genes, Variation in the mRNA and Intracellular Hsp Levels in COPD Secondary to Tobacco Smoking and Biomass-Burning Smoke. Front Genet 2020;10:1307.
81. Ünver R, Deveci F, Kırkıl G, Telo S, Kaman D, Kuluöztürk M. Serum Heat Shock Protein Levels and the Relationship of Heat Shock Proteins with Various Parameters in Chronic Obstructive Pulmonary Disease Patients. Turk Thorac J 2016;17:153-159.
82. Sangiorgi C, Vallese D, Gnemmi I, Bucchieri F, Balbi B, Brun P, *et al*. HSP60 activity on human bronchial epithelial cells. Int J Immunopathol Pharmacol 2017;30:333-340.
83. Ou G, Zhu M, Huang Y, Luo W, Zhao J, Zhang W, *et al*. HSP60 regulates the cigarette smoke-induced activation of TLR4-NF-κB-MyD88 signalling pathway and NLRP3 inflammasome. Int Immunopharmacol 2022;103:108445.
84. Kang Y, Wang F, Lu Z, Ying H, Zhang H, Ding W, *et al*. MAPK kinase 3 potentiates Chlamydia HSP60-induced inflammatory response through distinct activation of NF-κB. J Immunol 2013;191:386-94.
85. Eleftheriadis T, Pissas G, Liakopoulos V, Stefanidis I. Cytochrome c as a Potentially Clinical Useful Marker of Mitochondrial and Cellular Damage. Front Immunol 2016;7:279.
86. Puente-Maestu L, Pérez-Parra J, Godoy R, Moreno N, Tejedor A, Torres A, *et al*. Abnormal transition pore kinetics and cytochrome C release in muscle mitochondria of patients with chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 2009;40:746-50.
87. Zhang X, Li D, Wang H, Wu Y, Wen F. Elevated plasma cytochrome c levels in patients with chronic obstructive pulmonary disease. Current Science 2016;10:1532-1535.
88. Zeng H, Shi Z, Kong X, Chen Y, Zhang H, Peng H, *et al*. Involvement of B-cell CLL/lymphoma 2 promoter methylation in cigarette smoke extract-induced emphysema. Exp Biol Med (Maywood) 2016;241:808-16.
89. Ramage L, Jones AC, Whelan CJ. Induction of apoptosis with tobacco smoke and related products in A549 lung epithelial cells in vitro. J Inflamm (Lond) 2006;3:3.
90. Hosseini MJ, Naserzadeh P, Salimi A, Pourahmad J. Toxicity of cigarette smoke on isolated lung, heart, and brain mitochondria: induction of oxidative stress and cytochrome c release. Toxicol Environ Chem 2013; 95:1624-37.
91. Yang D, Xu D, Wang T, Yuan Z, Liu L, Shen Y, *et al*. Mitoquinone ameliorates cigarette smoke-induced airway inflammation and mucus hypersecretion in mice. Int Immunopharmacol 2021;90:107149.
92. Yang DQ, Zuo QN, Wang T, Xu D, Lian L, Gao LJ, *et al*. Mitochondrial-Targeting Antioxidant SS-31 Suppresses Airway Inflammation and Oxidative Stress Induced by Cigarette Smoke. Oxid Med Cell Longev 2021;2021:6644238.
93. Wenceslau CF, McCarthy CG, Goulopoulou S, Szasz T, NeSmith EG, Webb RC. Mitochondrial-derived N-formyl peptides: novel links between trauma, vascular collapse and sepsis. Med Hypotheses 2013;81:532-5.
94. Dorward DA, Lucas CD, Doherty MK, Chapman GB, Scholefield EJ, Conway Morris A, *et al*. Novel role for endogenous mitochondrial formylated peptide-driven formyl peptide receptor 1 signalling in acute respiratory distress syndrome. Thorax 2017;72:928-36.
95. Lubkin DT, Bishawi M, Barbas AS, Brennan TV, Kirk AD. Extracellular Mitochondrial DNA and N-Formyl Peptides in Trauma and Critical Illness: A Systematic Review. Crit Care Med 2018;46:2018-28.
96. Zhang X, Wang T, Yuan ZC, Dai LQ, Zeng N, Wang H, *et al*. Mitochondrial peptides cause proinflammatory responses in the alveolar epithelium via

FPR-1, MAPKs, and AKT: a potential mechanism involved in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2018;315:L775-86.
97. Atzori L, Lucattelli M, Scotton CJ, Laurent GJ, Bartalesi B, De Cunto G, *et al*. Absence of proteinase-activated receptor-1 signaling in mice confers protection from fMLP-induced goblet cell metaplasia. Am J Respir Cell Mol Biol 2009;41:680-7.
98. Yao H, Yang SR, Edirisinghe I, Rajendrasozhan S, Caito S, Adenuga D, *et al*. Disruption of p21 attenuates lung inflammation induced by cigarette smoke, LPS, and fMLP in mice. Am J Respir Cell Mol Biol 2008;39:7-18.
99. Wenceslau CF, Szasz T, McCarthy CG, Baban B, NeSmith E, Webb RC. Mitochondrial N-formyl peptides cause airway contraction and lung neutrophil infiltration via formyl peptide receptor activation. Pulm Pharmacol Ther. 2016;37:49-56.
100. He HQ, Ye RD. The Formyl Peptide Receptors: Diversity of Ligands and Mechanism for Recognition. Molecules 2017;22:455.
101. Lee HY, Lee M, Bae YS. Formyl Peptide Receptors in Cellular Differentiation and Inflammatory Diseases. J Cell Biochem 2017; 118:1300-7.
102. Yang SC, Hwang TL. The potential impacts of formyl peptide receptor 1 in inflammatory diseases. Front Biosci (Elite Ed). 2016;8:436-49.
103. Kwon WY, Suh GJ, Jung YS, Park SM, Oh S, Kim SH, *et al*. Circulating mitochondrial N-formyl peptides contribute to secondary nosocomial infection in patients with septic shock. Proc Natl Acad Sci U S A 2021; 118:e2018538118.
104. Yuan ZC, Zeng N, Liu L, Wang T, Dai LQ, Wang H, *et al*. Mitochondrial Damage-Associated Molecular Patterns Exacerbate Lung Fluid Imbalance Via the Formyl Peptide Receptor-1 Signaling Pathway in Acute Lung Injury. Crit Care Med 2021;49:e53-e62.
105. Li H, Itagaki K, Sandler N, Gallo D, Galenkamp A, Kaczmarek E, *et al*. Mitochondrial damage-associated molecular patterns from fractures suppress pulmonary immune responses via formyl peptide receptors 1 and 2. J Trauma Acute Care Surg 2015;78:272-9.
106. Cardini S, Dalli J, Fineschi S, Perretti M, Lungarella G, Lucattelli M. Genetic ablation of the fpr1 gene confers protection from smoking-induced lung emphysema in mice. Am J Respir Cell Mol Biol 2012; 47:332-9.
107. Gao L, Zeng N, Yuan Z, Wang T, Chen L, Yang D, *et al*. Knockout of Formyl Peptide Receptor-1 Attenuates Cigarette Smoke-Induced Airway Inflammation in Mice. Front Pharmacol 2021;12:632225.
108. De Cunto G, Bartalesi B, Cavarra E, Balzano E, Lungarella G, Lucattelli M. Ongoing Lung Inflammation and Disease Progression in Mice after Smoking Cessation: Beneficial Effects of Formyl-Peptide Receptor Blockade. Am J Pathol 2018;188:2195-206.
109. Bozinovski S, Anthony D, Anderson GP, Irving LB, Levy BD, Vlahos R. Treating neutrophilic inflammation in COPD by targeting ALX/FPR2 resolution pathways. Pharmacol Ther 2013;140:280-9.
110. Chen YC, Lin MC, Lee CH, Liu SF, Wang CC, Fang WF, *et al*. Defective formyl peptide receptor 2/3 and annexin A1 expressions associated with M2a polarization of blood immune cells in patients with chronic obstructive pulmonary disease. J Transl Med 2018;16:69.
111. Hsiao HM, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, Fulton RA, *et al*. A novel anti-inflammatory and pro-resolving role for resolvin D1 in acute cigarette smoke-induced lung inflammation. PLoS One 2013; 8:e58258.
112. Kim KH, Park TS, Kim YS, Lee JS, Oh YM, Lee SD, *et al*. Resolvin D1 prevents smoking-induced emphysema and promotes lung tissue regeneration. Int COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1119-28.
113. Possebon L, Costa SS, Souza HR, Azevedo LR, Sant'Ana M, Iyomasa-Pilon MM, *et al*. Mimetic peptide AC2-26 of annexin A1 as a potential therapeutic agent to treat COPD. Int Immunopharmacol 2018;63:270-81.
114. Wu Y, Qin J, He J, Shen Y, Wang H, Li Y, *et al*. Serum Endostatin Is a Novel Marker for COPD Associated with Lower Lung Function, Exacerbation and Systemic Inflammation. Int J Chron Obstruct Pulmon Dis 2020;15:397-407.
115. Chen J, Dai L, Wang T, He J, Wang Y, Wen F. The elevated CXCL5 levels in circulation are associated with lung function decline in COPD patients and cigarette smoking-induced mouse model of COPD. Ann Med 2019; 51:314-29.
116. Li D, Wu Y, Guo S, Qin J, Feng M, An Y, *et al*. Circulating syndecan-1 as a novel biomarker relates to lung function, systemic inflammation, and exacerbation in COPD. Int J Chron Obstruct Pulmon Dis 2019; 14:1933-41.

How to cite this article: Shen Y, Chen L, Chen J, Qin J, Wang T, Wen F. Mitochondrial damage-associated molecular patterns in chronic obstructive pulmonary disease: Pathogenetic mechanism and therapeutic target. J Transl Int Med 2023; 11: 330-340.