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REVIEW

Role of mitochondrial stress and the NLRP3 inflammasome in lung diseases

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Abstract

Background As an organelle essential for intracellular energy supply, mitochondria are involved in intracellular metabolism and inflammation, and cell death. The interaction of mitochondria with the NLRP3 inflammasome in the development of lung diseases has been extensively studied. However, the exact mechanism by which mitochondria mediate the activation of the NLRP3 inflammasome and trigger lung disease is still unclear.

Methods The literatures related to mitochondrial stress, NLRP3 inflammasome and lung diseases were searched in PubMed.

Results This review aims to provide new insights into the recently discovered mitochondrial regulation of the NLRP3 inflammasome in lung diseases. It also describes the crucial roles of mitochondrial autophagy, long noncoding RNA, micro RNA, altered mitochondrial membrane potential, cell membrane receptors, and ion channels in mitochondrial stress and regulation of the NLRP3 inflammasome, in addition to the reduction of mitochondrial stress by nuclear factor erythroid 2-related factor 2 (Nrf2). The effective components of potential drugs for the treatment of lung diseases under this mechanism are also summarized.

Conclusion This review provides a resource for the discovery of new therapeutic mechanisms and suggests ideas for the development of new therapeutic drugs, thus promoting the rapid treatment of lung diseases.

Keywords NLRP3 inflammasome · Mitochondria · Lung diseases · Oxidative stress · Potential drugs

Introduction

The human innate immune response, as the first line of defense against pathogenic invasion, is initiated by the pattern recognition receptor encoded by germline genes [1]. Pathogenic organisms are identified by pathogen-associated molecular patterns, in which a series of inflammatory responses are triggered to eliminate the associated pathogen or microbial infection to repair damaged tissue [2]. Since they were first proposed in 2002, inflammasomes have received widespread attention from the scientific community, which found that the NLRP3 inflammasome plays an important role as the core of the inflammatory response [3]. NLRP3 inflammasomes comprise complex protein bodies assembled from sensor protein NLRP3, adaptor protein of apoptosis-associated speck-like protein (ASC), and effector protein caspase-1 [4, 5]. Sensor protein NLRP3 is composed of three structural domains: a leucine-rich repeat (LRR) sequence, a central nucleotide-binding NACHT domain with ATPase activity, and an N-terminal pyrin domain (PYD) [6]. When external stimuli attack, sensor protein NLRP3 recruits ASC, forming a PYD–PYD structural domain with the PYD in ASC that results in the aggregation of ASC into ASC specks [7]. ASC specks then recruit the effector protein pro-caspase-1, binding to the caspase recruitment domain (CARD) in pro-caspase-1 to form a CARD-CARD structural domain. Eventually, the NLRP3 inflammasome is formed, which further activates caspase-1 [8, 9] to promote the maturation of interleukin (IL)-1β and IL-18, and shears

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Gasdermin D (GSDMD). Additionally, the N-terminal domain of GSDMD is then transferred to the cell membrane to form pores, leading to the release of cell contents and pyroptosis [10].

Currently, the NLRP3 inflammasome is understood to be mainly activated by two types of signals: a primary signal and an activation signal [11]. Toll-like receptors (TLRs), cytokine receptors, nucleotide-binding domain and LRR-containing (NLR) ligands, and other factors located on the cell membrane act as the primary signal to activate nuclear factor NF-κB into the nucleus, further promoting expression of NLRP3, pro-IL-18, and pro-IL-1β [12, 13]. Activation signals, such as reactive oxygen species (ROS), lysosomal damage, K^+ efflux, Ca^{2+} inward flow, and ATP, have all been shown to promote the assembly and activation of the NLRP3 inflammasome [14, 15]. The activated inflammasome promotes caspase-1 activation and further promotes the maturation of pro-inflammatory factors and pyroptosis (Fig. 1) [16]. Therefore, aberrant expression of the NLRP3 inflammasome can trigger inflammatory damage in the body. Such aberrant expression has been identified in many types of lung disease, including chronic obstructive pulmonary disease (COPD), lung cancer, acute lung injury (ALI), pulmonary fibrosis, and others (Fig. 2).

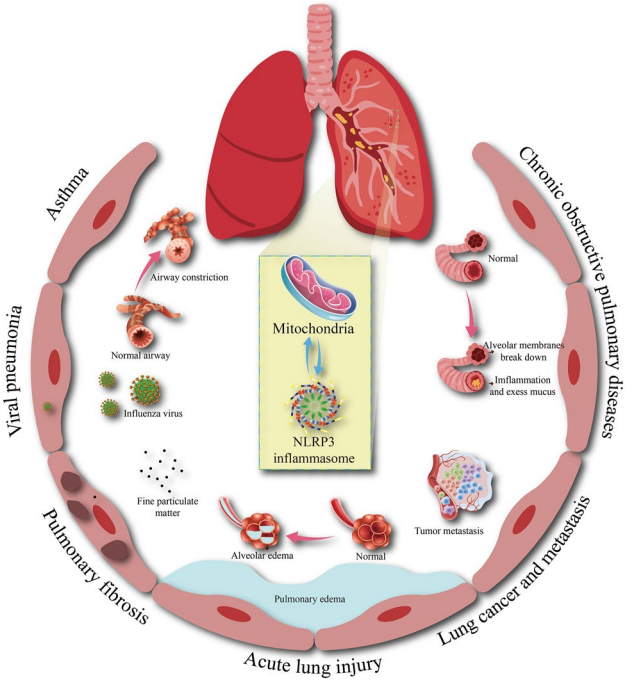

Fig. 2 Mitochondrial stress and the NLRP3 inflammasome mediate lung disease

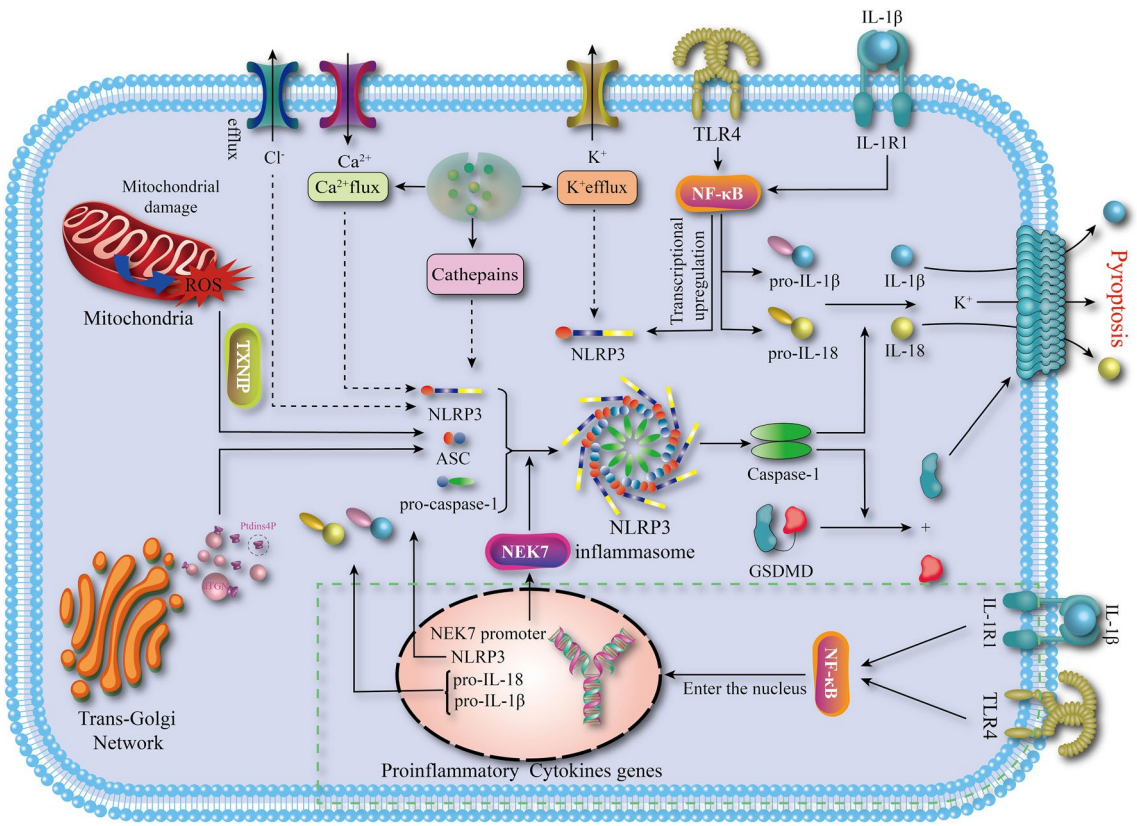

Fig. 1 Activation and assembly of the NLRP3 inflammasome. NIMA-related kinase 7 (NEK7); Thioredoxin-Interacting Protein (TXNIP)

Mitochondria are bilayer membrane organelles that provide energy for various cellular biological activities and are present in most cells, with participatory roles in cell proliferation, differentiation, senescence, apoptosis, and other processes [17]. Mitochondrial energy production requires extensive oxidative phosphorylation. During this process, the electron transport chain is blocked and part of the oxygen undergoes incomplete reduction to produce toxic substances, including superoxide anions, hydrogen peroxide and hydroxyl radicals [18, 19]. These substances are partially converted into ROS, and comprise the primary source of endogenous ROS production [20]. Additionally, compared with nuclear DNA, mitochondrial DNA (mtDNA) is more sensitive to oxidative stress [21]. Damage to mtDNA leads to mitochondrial dysfunction, in which mitochondrial double-stranded RNAs (mt-dsRNAs) are highly expressed and released extracellularly, leading to innate immune activation [22]. In response to stimulation, mitochondria can be induced to divide by mitochondrial fission factor (Mff) and dynamin-related protein 1 (Drp1). Alternatively, cells rely on mitofusin-2 (Mfn2) and optic atrophy 1 (OPA1) to fuse neighboring mitochondria and regulate mitochondrial kinetic balance [23]. In contrast, protein kinase R (PKR), a major sensor of mitochondrial stress-mediated cell death, recognizes most of the mt-dsRNAs [24]. Mt-dsRNAs activate PKR autophosphorylation and inhibit translation, while activating the release of inflammasome and pro-inflammatory factors, disrupting cellular homeostasis. Autophagy not only prevents the activation of PKR but also removes intracytoplasmic mt-dsRNAs, thus reducing the damage to the organism from mitochondrial stress [25]. Additionally, autophagy is involved in regulating dynamic homeostasis and can effectively remove damaged mitochondria from the cell. In damaged mitochondria, PTEN-induced putative kinase 1 (PINK1) accumulates on the outer mitochondrial membrane, marking the mitochondria for removal. After undergoing auto-phosphorylation, PINK1 recruits the E3 ligase Parkin, which ubiquinates mitochondrial outer membrane proteins and triggers the mitophagic process [26], removing excess mtROS, mtDNA and other substances that cause physiological reactions. In summary, in addition to giving the cell energy, mitochondria are crucial in cellular physiological activities. The link between mitochondria and the NLRP3 inflammasome has been widely studied in lung diseases, and it includes mitochondrial ROS (mtROS) and DNA (mtDNA), mitochondrial autophagy, and mitochondrial membrane proteins [27, 28], each of which is associated with activation of the NLRP3 inflammasome. However, it is not yet apparent how mitochondria and the NLRP3 inflammasome function to mediate lung disease onset and progression. Therefore, this review aims to clarify the role of mitochondrial stress and NLRP3 inflammasome in lung diseases to find new strategies for prevention and treatment.

Role of mitochondrial stress and the NLRP3 inflammasome in COPD

Mitochondrial dynamics and the effect of the NLRP3 inflammasome on COPD

COPD has become the third leading cause of death globally, affecting 250 million people and imposing a serious burden on society [29]. The chief features of COPD are irreversible airflow obstruction and airway inflammation, and the core susceptibility factor is oxidative stress [30]. Currently, no effective therapeutic drugs are able to prevent the decline in lung function in COPD over the long term. The main intracellular source of ROS, mitochondrial dysfunction, plays a significant role in the emergence of COPD. Mitochondrial function is regulated by fusion of healthy mitochondrial fragments to generate new mitochondria, and fission to remove damaged mitochondria [31]. Low levels of particulate matter (PM) ≤ 10 μm affect mitochondrial fusion and fission by precisely regulating the protein levels of OPA1 and Drp1. As a result of decreased levels of microtubule-associated protein 1A/1B light chain 3 (LC3)-II and phosphorylated AMP-activated protein kinase (AMPK), the NLRP3 inflammasome is activated, leading to inflammation in the lung [32]. Furthermore, using the cigarette smoke (CS)-induced COPD model, the expression of mitochondrial splitting proteins Mff and Drp1, caspase-1 and NLRP3 was discovered to increase, while the expression of mitochondrial fusion proteins Mfn2 and OPA1 dropped. Furthermore, these phenomena were reversed by pharmacological inhibition or knockdown of transient receptor potential cation subfamily V member 4 (TRPV4), TRPV1, or transient receptor potential cation channel member A1 (TRPA1) [33, 34]. TRPV4, TRPV1, and TRPA1 evidently alleviate CS-induced mitochondrial damage and NLRP3 inflammasome activation, suggesting that these channels are promising targets for new COPD treatments. Additionally, CS-induced oxidative stress on the endoplasmic reticulum has been reported to lead to disruption of endoplasmic reticulum calcium homeostasis. ROS production is then induced in mitochondria, which activates the NLRP3 inflammasome [35]. Furthermore, the same study showed that melatonin can reduce the accumulation of sequestosome 1 (p62/SQSTM1) by upregulating the expression of PINK1, Parkin and the autophagy marker LC3B-II. Autophagic breakdown of the injured mitochondria is induced, which inhibits the formation of mtROS and further decreases the activation of the NLRP3 inflammasome. However, in one study, excessive autophagy worsened the mitochondrial damage and

contributed negatively to the injury of human umbilical vein endothelial cells [36]. These results were corroborated using the mitochondrial antioxidant mitoquinone, which was found to reduce mtROS production and excessive autophagy. The preservation of mitochondrial function allowed for restoration of the endothelial barrier function and a decrease in the NF-κB/NLRP3-mediated inflammatory response. Clarification of the specific mechanism of autophagy in COPD caused by CS will require further investigation.

Effect of endogenous antioxidants and the NLRP3 inflammasome on COPD

ROS act primarily as activators in bronchial epithelial cell pyroptosis and acute exacerbation of COPD, activating the NLRP3 inflammasome and exacerbating disease progression [37, 38]. Compared with Nrf2 pathway, nuclear factor erythroid 2-related factor 2 (Nrf2) has a distinct advantage as an endogenous antioxidant pathway for the scavenging of ROS in vivo. Studies have shown that the amelioration of COPD inflammation by either (-)-epicatechin or the lipoxin receptor agonist BML-111 was exerted by upregulating the expression level of Nrf2 and attenuating the ROS/NLRP3/caspase-1 pathway [39, 40]. What is unique about (-)-epicatechin is that it reduces ubiquitination of Nrf2 by promoting tripartite motif-containing 25 (TRIM25)-mediated degradation of Kelch-like ECH-associated protein 1 (Keap1). The exact mechanism of BML-111 is unclear in that mtDNA also often acts as an activator of the NLRP3 inflammasome and is more vulnerable to oxidative damage than nuclear DNA [21]. Giordano et al. [29] found that sublethal amounts of CS not only caused an increase in mitochondrial membrane potential and dysregulation of mitochondrial dynamics, but also mediated the release of mtDNA from extracellular vesicles, triggering increases in NLRP3, pro-inflammatory factors and aging markers in cell cultures. These results were confirmed in the plasma of COPD patients. This study clearly suggested that DNA enzymes as therapeutic agents might be useful as a new therapeutic pathway for COPD patients.

Role of mitochondrial stress and the NLRP3 inflammasome in lung cancer

Impact of smoking and environment on lung cancer

Lung cancer stands out among other cancers because of its high mortality rate [41]. Currently, two types are recognized: small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC is the more common, accounting for approximately 85% of cases [42], and includes adenocarcinomas, squamous and large cell lung cancers [43]. According to multiple studies, lung cancer is the primary malignancy diagnosed in 11.6% of cases and the leading cause of death from cancer in 18.4% of cases. In high-income countries, lung cancer is 10 times more likely to develop in heavy smokers than in non-smokers, with non-smokers having a 1%–2% lifetime probability of developing lung cancer [44]. By contrast, in low-income countries, the number of lung cancer diagnoses continues to increase because of higher levels of exposure to environmental pollution and secondhand smoke [45, 46]. Currently, early surgical resection is the primary method of treating NSCLC (e.g., lobectomy). For nonsurgical patients, stereotactic radiotherapy and percutaneous thermal ablation procedures are used to treat advanced NSCLC [47]. Despite the fact that treatments for lung cancer have advanced quickly in the past 10 years, clinical outcomes for the disease remain unsatisfactory. Therefore, seeking new therapeutic agents and elucidating their molecular mechanisms against lung cancer are urgently important.

Effect of mitochondrial stress and the NLRP3 inflammasome on smoking- or silica-induced lung cancer

Mitochondria, as important mediators of cellular metabolism, induce apoptosis under a dysregulated state. In cancer cells in particular, ROS often play a regulatory role in inducing apoptosis [48]; however, the exact mechanism in lung cancer cells remains unclear. Studies have shown that CS is highly associated with lung cancer, and that benzo(a)pyrene (BaP) in cigarettes is one of the inducers of lung cancer. This led to the establishment of a lung cancer model induced by BaP, and a study examining treatment with IL-27 and IL-28B [49]. The results showed that IL-27 and IL-28B not only downregulated the expression of the NLRP3 inflammasome but also reduced the aggregation of ROS in lung cancer [50]. The combination downregulated ROS-mediated activation of ERK1/2 and inhibited mast cell aggregation in lung tissue, thus acting as a treatment for lung cancer. The link between silica and lung cancer risk is controversial [51]. A recent study showed that silica-induced DNA damage was not caused by high or low ROS levels, but it was determined by silica-induced NLRP3 phosphorylation and mitochondrial depolarization, which led to DNA damage. Furthermore, silencing NLRP3 with small interfering RNA and CRISPR Cas9 prevented mitochondria depolarization and protected against DNA damage [52]. Further studies revealed that mitochondrial depolarization was critical for triggering DNA damage and was largely dependent on phosphorylation of serine 198 of NLRP3. Nevertheless, Zheng et al. showed that silica could damage DNA through a different mechanism of action [53]. In their study, silica acting

on P2X7 induced mitochondrial production of ROS that activated the NLRP3 inflammasome, leading to the accumulation of double-strand breaks (DSBs). However, ataxia-telangiectasia mutated (ATM) activation of autotaxin (ATX) was dependent on the above process, which then triggered lung inflammation and DNA damage, resulting in the emergence of lung cancer. Taken together, these studies showed that both depolarization of mitochondrial membranes and activation of the ROS/NLRP3/ATX axis are closely related to lung carcinogenesis.

Effect of mitochondrial stress and the NLRP3 inflammasome on lung cancer migration

Malignant tumors are unsettling mostly because of their propensity for spreading, which also serves as the main cause of failure of tumor treatments. Therefore, the prevention of malignant tumor spread is often more important than treatment [54]. To examine whether bacterial infection could aggravate the development of lung cancer, Ma et al. [55] induced A549 cells with lipopolysaccharide (LPS) and discovered that LPS encouraged A549 cells to proliferate and migrate. They also found that salidroside, by promoting AMPK protein expression, suppressed NLRP3 inflammasome activation and ROS production, while also reducing the proliferation and migration of LPS-induced A549 cells. Ergosterol peroxide (EP) isolated from marine fungus *Phoma sp* was also shown to inhibit lung cancer migration [48]. In this study, EP induced A549 autophagy through mitochondrial damage, and this outcome was reversed by the ROS inhibitor N-acetylcysteine. EP also inhibited the activity of the NLRP3 inflammasome, thus reducing the proliferation and migration of lung cancer cells mediated by LPS. Additionally, EP synergized with the inhibition of A549 cell viability by the anti-cancer drug sorafenib. The biggest concern of breast cancer patients after surgery is the spread of the tumor, which is often directed to the more vascular organs; for example, breast cancer spreads to the lungs [56], which then spreads to other organs. Elemene nanoemulsion and hydrophilic As_4S_4 nanoparticles not only clear ROS, but also prevent NLRP3 inflammasome bodies from activating both in vitro and in vivo, and efficiently prevent breast cancer cells from spreading to the lungs, thus reducing the spread of cancer [57, 58]. Inhibiting the spread of a tumor to the lungs is a priority.

Antioxidant and anti-lung cancer effects of natural drugs on mitochondria and the NLRP3 inflammasome

In recent years, natural drugs, with their good therapeutic effects and few toxic side effects, have gradually come to play an important role in cancer treatment [59]. This is especially true in lung cancer treatment, which is currently limited to drugs with highly toxic side effects and thus in urgent need of new therapeutics. Studies have shown that most drugs activate NF-κB entry into the nucleus by regulating ROS levels in cells, causing the NLRP3 inflammasome to assemble and become active, and then increase caspase-1 protein expression to mediate lung cancer pyroptosis [60–62]. However, their mechanisms for regulating intracellular oxidative stress are very different. For example, by inhibiting the expression of glutathione peroxidase 4 (GPX4) and depolarizing mitochondrial membranes, shiitake polysaccharide alters the oxidative state of lung cancer cells [63]. Shiitake polysaccharide also downregulates the long noncoding RNA encoded by the X inactive-specific transcript (LncRNA-XIST) gene, which is highly expressed in lung cancer tissues, thereby promoting the Mn superoxide dismutase (Mn-SOD)-mediated increase in ROS levels and apoptosis [64]. Another natural drug, cucurbitacin B, reportedly exerts its antitumor activities via binding to Toll-like receptor 4 (TLR4) which leads to elevated mtROS levels, accumulation of mitochondrial membrane protein Tom20, and the release of cytoplasmic Ca^{2+} [15]. In summary, lung cancer development is significantly influenced by the activation of the NLRP3 inflammasome and mitochondrial oxidative stress. According to ongoing studies, the development of future lung cancer treatments will increasingly focus on the NLRP3 inflammasome and mitochondrial oxidative stress as key targets.

Mitochondrial stress and role of the NLRP3 inflammasome in acute lung injury

Oxidative stress and acute lung injury

The COVID-19 pandemic has been an unprecedented catastrophe for the world. COVID-19 mainly causes pulmonary complications such as pneumonia. Severe pneumonia can rapidly develop into acute respiratory distress syndrome or ALI [65]. However, the drugs currently used to treat ALI, which include vasodilators, ketoconazole and antioxidant therapy [66], are not specific or efficacious for ALI, despite some advancements in the field [67]. Therapeutics that counter oxidative stress and promote anti-inflammatory responses are expected to be a breakthrough in the treatment of ALI.

Amelioration of ALI by inhibiting mtROS and NLRP3 inflammasome activation

Mitochondria, as a major source of endogenous oxidative stress in cells, occupy a significant position in the body's response to oxidative stress and inflammation [68]. Studies have shown that renal ischemia–reperfusion-induced ALI alters mitochondrial membrane potential as well as mitochondrial morphology [69]. NaHS and dexmedetomidine effectively reduced inflammatory factor levels by inhibiting NLRP3 inflammasome activation, which prevented mitochondrial damage, morphological and structural alterations, and mitochondrial dysfunction, thereby inhibiting mtROS production [70, 71]. Furthermore, cases of ALI caused by acid or bacterial inhalation were shown to exhibit elevated levels of mtROS and reduced aconitase activity as a superoxide anion-sensitive enzyme [72]. The administration of Mito-TEMPO revealed that NLRP3 inflammasome activation was inhibited and expression of IL-1β, TNF-α and IL-6 was downregulated [73]. These results suggest that mtROS cause ALI by precisely mediating the NLRP3 inflammasome; hence, targeted inhibition of mtROS may be one key to treating ALI. Endogenous antioxidants are also critical for the treatment of ALI. Melatonin reduces the generation of mtROS by activating the Nrf2/HO-1 pathway and increasing the expression of Mn-SOD and NAD(P)H:quinone oxidoreductase 1 (NQO1), which prevents the release of inflammatory factors and reverses the upregulation of NLRP3 and caspase-1 brought on by LPS. These effects of melatonin were also shown to reduce the occurrence of pyroptosis [74]. Additionally, calycosin [75] has been found to raise SOD and glutathione (GSH) levels in lung tissue while suppressing NLRP3 inflammasome activation and preventing the interaction of NLRP3, ASC and caspase-1. Notably, all of these effects are mediated through the regulation of mtROS, indicating that the NLRP3 inflammasome is inextricably activated by mtROS. Consequently, recent research on mitochondrial oxidative stress in ALI has been relatively shallow and mainly focused on pharmacological antioxidant studies. For example, drugs that treat or protect against ALI by inhibiting the ROS-mediated TXNIP/NLRP3 [76–78], TLR4/TRAF6 [79] and TRPM2/$Ca2^{+}$/NLRP3 axes, or by activating the Nrf2/HO-1/NQO1 axis [80–82], reduce intracellular ROS levels to further decrease NLRP3 activation. Medications that suppress the NLRP3 inflammasome pathway via reduction of oxidative stress (Table 1) are characterized by mainly natural plant components. With further research, they will hopefully become a new approach to preventing or effectively treating ALI.

Potential mitochondrial targets and improvement of ALI via the NLRP3 inflammasome

Autophagy selectively clears damaged mitochondria, which negatively regulates mtROS production and inflammasome activation [83]. The regulation of autophagy in LPS-induced ALI was found to be worsened by a faulty FUNDC1 gene, which encodes a mitochondrial outer membrane protein, as shown by significant elevations in ROS, NLRP3, caspase-1 and inflammatory markers, along with significant inhibition of autophagy in lung tissue [84]. Sestrin2 (*sesn2*) showed the same phenomenon: knockdown of *sesn2* led to upregulated mtROS expression levels and inhibition of mitochondrial autophagy [85]. Thus, lung cell pyroptosis appears to result from excessive promotion of NLRP3 inflammasome activation. These studies also demonstrated that FUNDC1 and Sestrin2 mediate mitochondrial autophagy and are vital for the modulation of mtROS, which might represent a viable therapy for ALI. Additionally, ROS cause elevated levels of lipid peroxides, possibly leading to iron-dependent death, which is mainly characterized by increased membrane density and rupture, and mitochondrial atrophy [86]. Expression of the iron death biomarker GPX4 was decreased, while expression of prostaglandin endoperoxidase synthase 2 (PTGS2) was increased, in ALI [87, 88]. Furthermore, mitochondrial acetaldehyde dehydrogenase 2 (ALDH2) expression inhibited iron-dependent death and pyroptosis, exerting a protective effect against ALI [89]. Clearly, iron-dependent cell death is involved in the ALI process. Sirtuin-3 (SIRT3), a mitochondrial NAD + deacetylase, plays a key role in inflammation regulation and lung injury. Pro-inflammatory factors are major players in ALI and are important treatment targets [67]. PKR acts as a stressor for mt-dsRNAs, its activation significantly increases the expression of IL-1β and high mobility group box-1 protein (HMGB1) [90], and it interacts with NLRP3 to activate the NLRP3 inflammasome [91]. These functions suggest inhibition of PKR expression as a potential strategy for the treatment of ALI. SIRT3 deficiency disrupted mitochondrial redox homeostasis, activating the NLRP3 inflammasome and leading to inflammation. While administration of the SIRT3 activator viniferin can attenuate ALI in wild-type mice, it is not effective in SIRT3-deficient mice [92]. Therefore, PKR has a role in the development of ALI, either by mediating mitochondrial autophagy or regulating the expression of PTGS2, SIRT3, or PKR, and it is expected to be a key target in the treatment of ALI.

Table 1 Improvement of ALI by drugs that impact oxidative stress and the NLRP3 inflammasome

Therapeutic drugs	Oxidative stress and the role of NLRP3 inflammasome	Experimental model	References
Apelin-13	Inhibition of ROS formation and mitochondrial damage, prevention of NF-κB/NLRP3 protein activation	Adult male C57BL/6N mice were given an intratracheal injection of LPS to create an ALI model	[69]
NaHS	Inhibition of NLRP3 inflammasome activation by improving mitochondrial function and activating the Nrf2 pathway	Establishment of renal ischemia–reperfusion model using bilateral renal artery clamping in wild-type and Nrf2-/- C57BL/6 J mice	[70]
Dexmedetomidine	Inhibition of HMGB1, ASC and NLRP3 production and improvement of AMPK signaling pathway	Serum incubation AM in renal ischemia–reperfusion rats to establish an in vitro renal ischemia–reperfusion-mediated ALI model	[71]
Calycosin	The inflammasome's ability to become activated by mitochondrial ROS is inhibited by calycosin	Induction of ALI model in male C57BL/6 mice using LPS and cecal ligation and puncture	[75]
Linarin	Inhibition of XO/TXNIP/NLRP3 and NF-κB pathways and inhibiting oxidative stress and inflammatory responses	To create an ALI model, intranasal LPS was administered to C57BL/6 mice	[76]
NecroX-5	Downregulation of TXNIP/NLRP3 and NF-κB pathways and suppression of inflammatory factor expression levels	Male C57BL/6 mice were injected with LPS intravenously to create a model for acute lung injury	[77]
Vitexin	Modulation of the Nrf2 pathway eliminates ROS to inhibit NLRP3 inflammasome activation	LPS intravenous infusion causes ALI in C57BL/6 mice	[80]
PKR inhibitor ($C_{13}H_8N_4OS$)	Inhibition of PKR phosphorylation downregulates NLRP3 inflammasome and inflammatory factor expression	Male C57BL/6 mice were anesthetized with ether to establish an ALI model by intra-tracheal injection of LPS	[91]
Apocynin	Downregulation of NF-κB/NLRP3 pathway through inhibition of NADPH oxidase signaling pathway	Severe acute pancreatitis induced by sodium taurocholate, triggering ALI model	[93]
Diosmetin	Activation of Nrf2 scavenges ROS and inhibition NLRP3 inflammasome	Adult female BALB/c mice, intranasal injection of LPS to establish ALI model	[94]
Procyanidin B2	Upregulation of SOD and inhibition of NLRP3 inflammasome	Establishment of ALI model by intraperitoneal injection of paraquat in male Sprague Dawley rats	[95]
2-Succinate-Anthraquinone	Downregulation of NLRP3 signaling pathway, inhibition of oxidative stress and THP-1 macrophage migration	In vivo inflammatory model induced by LPS injection in C57BL/6 mice	[96]
Isoliquiritigenin	Activation of AMPK/Nrf2/ARE signaling pathway and inhibition of NLRP3 as well NF-κB activation	Establishment of ALI model by intranasal injection of LPS in wild-type and Nrf2-/- C57BL/6 mice	[97]
Fe–curcumin-based nanoparticles	Scavenging intracellular ROS and reducing calcium ion release, inhibiting NLRP3 inflammasome and NF-κB signaling pathway	LPS/ATP-induced ALI model in mice	[98]
Curcumin	The inflammasome pathway TXNIP/NLRP3 is prevented from being activated by ROS	Paraquat inducing normal lung fibroblasts (WI-38 V A13) injury to establish an in vitro ALI model	[99]
Chicoric acid	Activation of Nrf2 pathway and inhibition of MAPK and NLRP3 activation	Male BALB/c mice with the intranasal injection of LPS-induced ALI model	[100]
Epoxyeicosatrienoic acids	Suppression of NLRP3 inflammasome activation through inhibition of intracellular Ca^{2+} excess and ROS generation	Male C57BL/6 mice were injected with LPS intravenously to create a model for acute lung injury	[101]

Role of mitochondrial stress and the NLRP3 inflammasome in pulmonary fibrosis

Pathogenic characteristics of pulmonary fibrosis

Pulmonary fibrosis manifests as fibroblast proliferation and massive extracellular matrix aggregation, with inflammatory injury and tissue structural damage [102]. Because the etiology is absent in the vast majority of patients with pulmonary fibrosis, the most prevalent form of which is idiopathic pulmonary fibrosis, the condition is known as idiopathic interstitial pneumonia. Currently, there is no effective treatment and a high mortality rate for idiopathic pulmonary fibrosis [103]. We must urgently elucidate the pathophysiologic mechanisms and seek effective therapeutic drugs.

Effect of mitochondrial autophagy and the NLRP3 inflammasome on pulmonary fibrosis

In pulmonary fibrosis, the abnormal expression of mtROS induces mtDNA damage, which in turn activates macrophages and fibroblasts [104]. Therefore, ROS production and mtDNA damage are considered to be main features of pulmonary fibrosis. Sakai et al. [105] developed the cytoplasmic ·OH and mitochondrial ·OH scavengers TA293 and MitoTA293 to study this phenomenon. They demonstrated that cytoplasmic ·OH depleted intracellular GSH content, which triggered a decrease in mitochondrial GSH content and further induced H_2O_2 production in mitochondria, damaging the mtDNA and activating the NLRP3 inflammasome. In contrast, ·OH in mitochondria induced cell division and scavenged mtDNA in response to oxidative damage, consequently preventing the NLRP3 inflammasome from being activated and slowing the development of pulmonary fibrosis. Mn-SOD is a mitochondrial detoxifying agent that protects mitochondria from oxidative damage [106]. Anakinra, a recombinant IL-1 receptor antagonist, extended the lifespan of Mn-SOD by encouraging Mn-SOD binding with ubiquitin-specific protease 36 (USP36) and constitutive photomorphogenic 9 (COP9) signalosomes, thereby preventing oxidative damage to mitochondria and the generation of ROS, and avoiding the activation of the NLRP3 inflammasome [107].

Exosomal micro-RNA (miRNA) Let-7 has also been reported to control the expression of leptin-like oxidized low-density lipoprotein receptor-1 (LOX1) in lung epithelial cells, which in turn efficiently inhibits the formation of mtROS and DNA damage. Activation of the NLRP3 inflammasome and the process of pulmonary fibrosis were also inhibited [108]. However, more research is required to determine whether LOX1 may be a useful target for the therapy of pulmonary fibrosis. Pulmonary fibrosis occurs in response to apoptosis of damaged lung epithelial cells, which are subsequently phagocytosed and aggregated by macrophages [109]. Additionally, patients who experience exacerbations of acute idiopathic pulmonary fibrosis exacerbations also exhibit this phenomenon. Changes in both radiation-apoptotic lung cancer cells and microbiota were found that could activate the NLRP3 inflammasome by mediating mtROS; however, the former required cathepsin B involvement and the latter was associated with AIM2 inflammasome [48, 110]. Autophagy, similar to apoptosis, is a very important biological phenomenon in cells and is essential for the development of pulmonary fibrosis. Following its induction of redox imbalance, Ang II was shown to activate autophagy, which effectively reduced the quantity of ROS in cells, exacerbating pulmonary fibrosis [111]. Furthermore, the activation of autophagy was mainly dependent on the upregulation of NADPH oxidase-4 (NOX4) and its mediation of ROS/AMPK pathway activation, which decreased the accumulation of ROS [112]. Meanwhile, Ang II induced P62/SQSTM1 to degrade ubiquitinated ASC containing CARD, thereby inhibiting NLRP3 inflammasome activation and attenuating pulmonary fibrosis.

Effects of mitochondrial stress and the NLRP3 inflammasome on PM-induced pulmonary fibrosis

Although $PM_{2.5}$ is found at a low level in the air, it has received widespread attention because it contains a variety of substances that are harmful to humans [113] and has unique and complex physicochemical properties. By conditioning the physicochemical properties of $PM_{2.5}$, metal ions, polycyclic aromatic hydrocarbons and ROS in $PM_{2.5}$ were found to encourage the activation of the NLRP3 inflammasome and generated mtROS [62]. Intranasal instillation of $PM_{2.5}$ drops led to upregulation of NOX4 protein expression, increased levels of mtROS levels, and activation of the NLRP3 inflammasome in lung tissue after 3 weeks, and a fibrotic phenotype in the lung tissue after 9 weeks [112]. These results were attributed to mitochondrial damage and autophagy [114], and activation of the TGFβ1-NOX4-NLRP3 pathway. However, $PM_{2.5}$ is not the only airborne PM capable of triggering pulmonary fibrosis. Carbon nanotubes, and silica and carbon black nanoparticles are all involved in affecting mitochondrial membrane potential as well as ROS production [115, 116], but they activate the NLRP3 inflammasome in different ways. For example, carbon black nanoparticles regulate NLRP3

inflammasome activation through miRNA-96, targeting FOXO3a to trigger pulmonary fibrosis [117]. To develop animal models to research the prevention and management of pulmonary fibrosis, understanding the disease processes affected by such particles is essential, which is expected to be a challenge in overcoming lung diseases caused by environmental pollution.

Mitochondrial stress and role of the NLRP3 inflammasome in lung infection and other lung diseases

Mitochondrial stress and the NLRP3 inflammasome ameliorate viral pneumonia

Influenza virus is a highly infectious virus of the human respiratory tract, and numerous inactivated vaccines and antiviral medications have been created following considerable research [118]. However, human health remains at serious risk due to the high genetic variability and emergence of drug-resistant strains of the virus [119]. Therefore, studies on the pathogenic mechanism of influenza viruses and screening for antiviral drugs should continue. Mitochondrial dynamics have been shown to be closely related to the pathogenesis of influenza viruses [120]. In the swine influenza virus, increased expression of the receptor-interacting protein kinase 1 (RIPK1) resulted in phosphorylation of a serine at position 579 in Drp1, promoted mitochondrial division and caused activation of the NLRP3 inflammasome [121]. However, to treat influenza pneumonia, berberine was shown to block the activation of the NLRP3 inflammasome and promote mitochondrial autophagy through the Bcl-2/adenovirus E1B-19-kDa interacting protein 3 (BNIP3) pathway [122]. Additionally, inhibition of the calcium receptor stromal interaction molecule 1 (STIM1) reversed the lung injury caused by miRNA-233 and ROS upregulation induced by the influenza virus [123]. Moreover, PKR, as a key to the body's defense against viral infection [124], recognizes viral dsRNA, mediates the activation of MAPK and NF-κB signaling, and promotes the release of inflammatory factors [125, 126]. The adenovirus-5 virus-associated RNAi inhibits the activation of the NLRP3 inflammasome precisely by targeting PKR and inhibiting PKR auto-phosphorylation, while blocking PKR–ASC interaction [127]. Reduning combined with ribavirin also attenuates the pathological injury caused by severe influenza pneumonia, reportedly impacting the inhibition of NLRP3 activation, mostly through lowering ROS levels [128]. Therefore, NLRP3 inflammasome activation and modulation of the mitochondrial kinetic balance may be crucial components of future strategies to prevent or treat viral lung illnesses.

Mitochondrial stress and the NLRP3 inflammasome ameliorate asthma

Asthma, a common lung disease, has pathogenic and therapeutic mechanisms closely related to mitochondrial dynamics and NLRP3 inflammasome activation. Among the pathogenic mechanisms, ozone, as a potent oxidizing gas, is strongly linked to the emergence of a number of lung diseases [129], including airway inflammation with bronchial hyper-responsiveness. Acute ozone exposure was found to lead to upregulated expression of mitochondrial complex II and IV, and induced elevated expression of mitochondrial Drp1 and Mff, decreased Mfn2, and upregulated mtROS levels in lung tissue [130]. Thus, an imbalance in mitochondrial dynamics may be critical in triggering bronchial hyper-responsiveness. Controlling the production of asthmatic mucus can alleviate asthma [131]. Specifically, the aryl hydrocarbon receptor (AhR) effectively inhibits asthmatic mucus production by inhibiting NLRP3 inflammasome activation and reducing IL-1β expression via decreased mtROS levels [132], thereby avoiding the IL-1β-induced overexpression of mucin 5AC that leads to asthmatic mucus production and asthma exacerbation. One study revealed that patients with severe asthma exhibit mitochondrial malfunction and ROS aggregation [133] manifested by inhibition of the autophagy controller transcription factor EB (TFEB) signaling pathway. This inhibition results in diminished mitochondrial autophagy and the inability to clear damaged mitochondria, which activates the NLRP3 signaling pathway and exacerbates asthma. Therefore, the regulation of mitochondrial oxidative stress is crucial for the prevention and treatment of asthma.

Others

According to a growing body of research, oxidative stress and inflammasome activation are linked to increased lung inflammation [134–136]. Indeed, modulation of this pathway and inhibition of inflammasome activation have become effective therapeutic approaches (Table 2) in lung conditions, such as radiation pneumonia [137], pulmonary ischemia–reperfusion injury [138, 139], and chronic intermittent hypoxia [140]. Carbon monoxide releasing molecule-2 (CORM-2) was shown to not only decrease the expression of TLR2 and TLR4 but also restrain NADPH oxidase activity, thereby reducing mtROS production and exerting a protective effect against PM-induced lung inflammation [141]. In another example, resveratrol protected against nickel-induced pneumonia by reducing the accumulation of ROS [142]. The

Table 2 Therapeutic drug-mediated mitochondrial stress and the NLRP3 inflammasome in lung infections and other lung diseases

Disease type	Treatment drugs/methods	Treatment mechanism	Experimental model	References
Viral pneumonia	Berberine	Inducing mitochondrial autophagy and thereby reducing mtROS levels inhibits NLRP3 inflammasome activation	Establishment of viral pneumonia model by intranasal injection of PR8 influenza virus in BALB/c mice	[122]
Severe pneumonia	Reduning plus ribavirin	IL-1 and IL-18 cytokine levels, ROS generation, and NLRP3 inflammasome activation are all decreased	A severe pneumonia model for BALB/c mice was created by injecting the influenza A H1N1 virus intraperitoneally	[128]
Asthma	Aryl hydrocarbon receptor inhibitors	Epithelial aryl hydrocarbon receptor protects from mucus production by inhibiting ROS-triggered NLRP3 inflammasome in asthma	C57BL/6 J and AhR-/- mice were used as an asthma model produced by cockroach allergen	[132]
Pulmonary inflammation	Ethanolic extract of flowers of *Tussilago farfara L*	Activation of Nrf2 and inhibition of NF-κB and NLRP3 inflammasome	Inhalation of cigarette smoke in male C57BL/6N mice established a model of inflammatory damage	[135]
Pulmonary inflammation	18β-glycyrrhetinic acid	Inhibition of NF-κB and NLRP3 activation and reduction of ROS levels	Exposure of neonatal rats to a hyperoxic environment employing soda lime for CO_2 absorption led to lung inflammation	[136]
Pulmonary ischemia reperfusion	Cold ischemia phase hydrogen filling	Inhibiting ROS production, downregulating NLRP3, caspase-1, and GSDMD expression to prevent pyroptosis	Wistar rats were lung transplanted with O_2 and H_2 after lung extraction to establish a lung ischemia–reperfusion model	[138]
Pulmonary ischemia reperfusion	MCC950	Blocking the interaction between NLRP3 and Nek7	After opening the chest of male C57BL/6 mice, the lung hilum was clamped with a microvascular clip, and the clip was removed after 1 h. The chest cavity was closed to establish a lung ischemia–reperfusion model	[139]
Pulmonary inflammation	CORM-2	Downregulation of TLR2 and TLR4 expression and inhibition of ROS/NLRP3 axis	The PM suspension was placed in the throat of BALB/c mice and then inhaled by the mice autonomously to establish an inflammation model in the lungs	[141]
Nickel poisoning	Resveratrol	Reduced accumulation of ROS, thereby inhibiting p38MAPK, NF-κB and NLRP3 signaling channels	Administration of $NiCl_2$ to BEAS-2B cells established a cytotoxic model	[142]
Aspergillus fumigatus pulmonary infection	Allicin	Reduced spore activity and inhibition of ROS production, thereby reducing NLRP3 activation and autophagy	Intratracheal injection of aspergillus fumigatus spores in BALB/c mice, followed by intravenous injection of allicin to establish a therapeutic model	[146]
Melioidosis	Caspase-1 or caspase-11 agonists	Mediates pyroptosis and IL-18 production	Caspase-11-/- mice and caspase-1-/- mice were used to establish the model	[147]

important role of G protein-coupled receptor 43 (GPR43) in lung injury has also been confirmed at the molecular level, with upregulated GPR43 gene expression shown to inhibit NLRP3 inflammasome activation through the PPAR-gamma/Nox1/EBP50/p47phox axis, and thereby treat inflammatory responses to mitochondrial injury [143]. The role of oxidative stress with NLRP3 has also been confirmed in bacterial pneumonia. Furthermore, fungal β-glucan, *Glaesserella parasuis* and *Aspergillus fumigatus* were shown to induce inflammation in the lungs by regulating ROS levels and activating inflammasomes [144, 145]. The latter could be directly inhibited by allicin in terms of reduced spore activity and amelioration of lung inflammation by regulating expression of NLRP3 and caspase-1, and inhibiting excessive autophagy [146]. This study demonstrated how crucial the NLRP3 inflammasome and mitochondrial oxidative stress are to the inflammatory response, and we predict that continued research in this area will ultimately overcome the therapeutic challenges of lung disease.

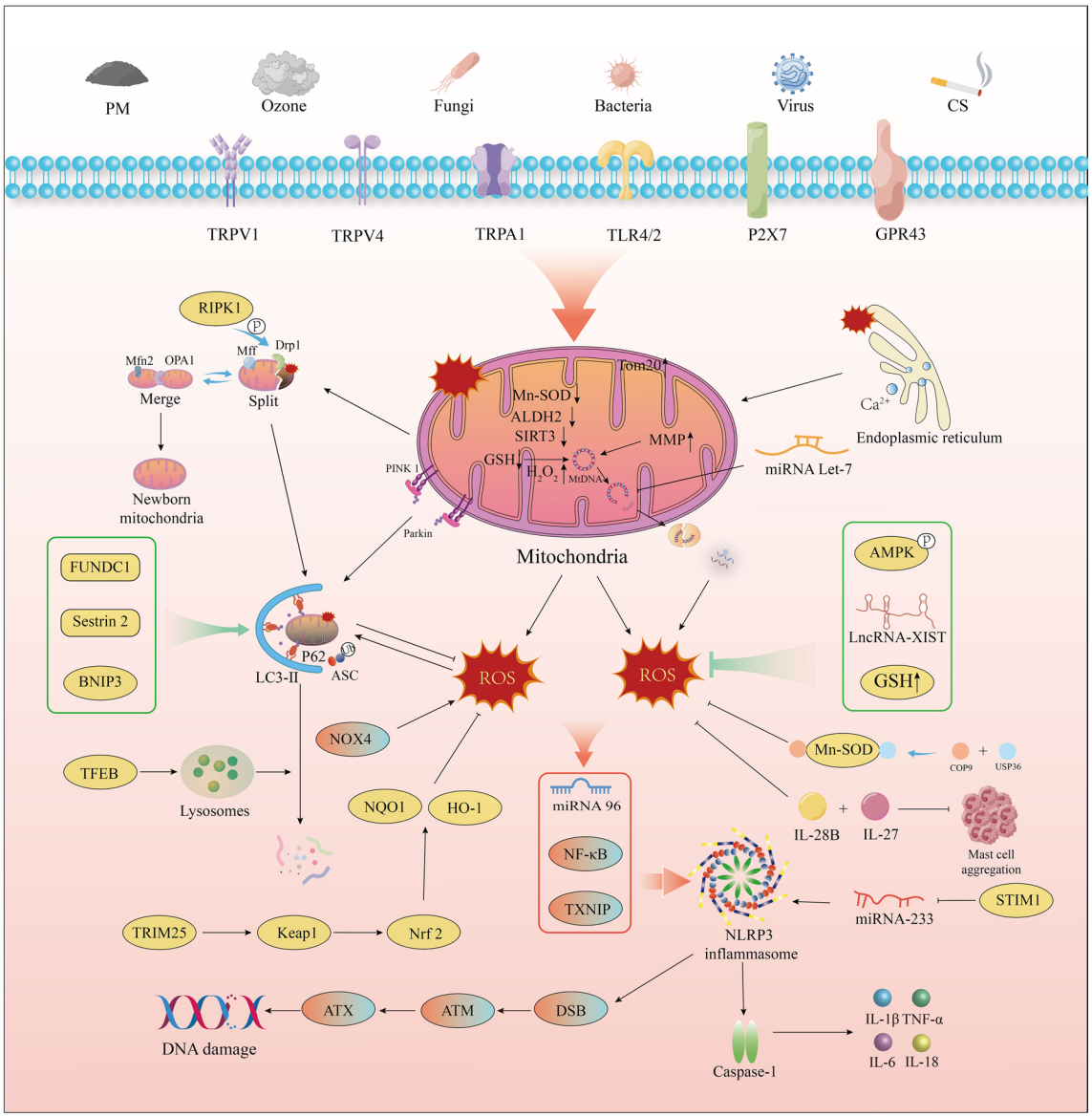

Fig. 3 Therapeutic mechanisms of mitochondrial stress and NLRP3 inflammasome activation in lung disease. Mitochondrial membrane potential (MMP)

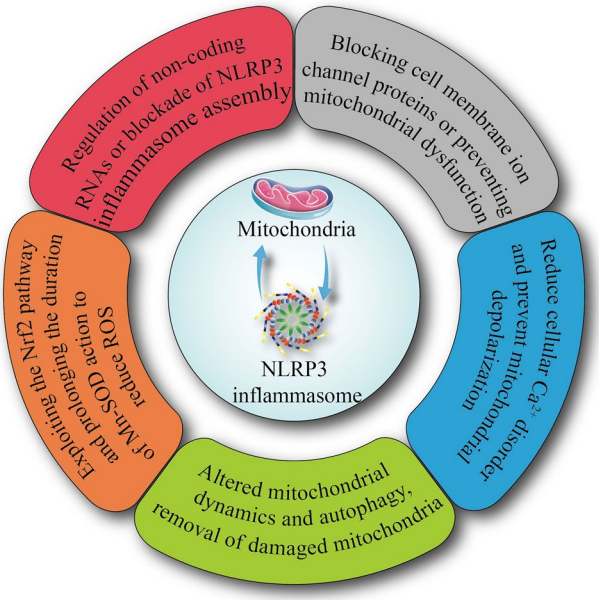

Fig. 4 Major treatment approaches for lung diseases

Conclusion

Mitochondria are intracellular multifunctional organelles that are crucial targets for the management of oxidative stress, inflammatory response, cancer and more. Mitochondrial dysfunction leads to a series of stress responses (Fig. 3), including alterations in mitochondrial membrane potential, Mn-SOD content, ALDH activity, Tom20 expression and mitochondrial dynamics. These changes serve as activation signals for the NLRP3 inflammasome, mediating mtROS and mtDNA with mt-dsRNAs, and altering the histopathological state of the lung. Therefore, removing damaged mitochondria and reducing the stress response triggered by mitochondrial dysfunction are two effective approaches to improving lung diseases. Currently, the main therapeutic approaches in lung disease can be divided into five areas (Fig. 4): (1) prevention of mitochondrial dysfunction by blocking ion channels or cell membrane proteins to diminish the stimulation of external factors; (2) inhibition of mtROS production by reducing intracellular Ca^{2+} disorder and decreasing mitochondrial depolarization; (3) alteration of intracellular mitochondrial dynamics, or increased mitochondrial autophagy to remove damaged mitochondria, to prevent ROS accumulation; (4) promotion of endogenous antioxidant pathways or prolongation of the duration of action of antioxidant proteins to reduce ROS accumulation and inhibit activation of the NLRP3 inflammasome; and (5) regulation of noncoding RNA expression, inhibition of mtDNA damage or mtROS production, or direct blockade of NLRP3 inflammasome assembly. Mitochondrial stress from an altered cellular environment is mainly manifested by mtROS production and mtDNA damage. Strategies to control mtROS generation and prevent NLRP3 inflammasome activation will undoubtedly become the focus of future treatments for lung disease.

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Data availability Not available.

Declarations

Conflict of interest The authors declare no conflict of interest.

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