Mitochondria and their potential role in acute lung injury (Review)

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Abstract. Acute lung injury (ALI) and its more serious form [acute respiratory distress syndrome (ARDS)] are devastating diseases that lead to high morbidity and mortality rates in patients in intensive care units. ALI is caused by numerous direct or indirect factors, including trauma and sepsis. However, the underlying mechanism associated with the pathophysiological process of ALI has yet to be fully elucidated. As our understanding of mitochondrial biology continuously progresses, mitochondria have been largely considered as biosynthetic, bioenergetic and signaling organelles that have a critical role in the processes of cellular development, proliferation and death, and novel insights into how mitochondrial dysfunction affects the pathogenesis of different diseases have been garnered. According to current research models, functional characteristics of mitochondria are recognized to affect the function of cells and organs in ALI. The aim of the present review is therefore to discuss mitochondria and their role in ALI, and to consider how they may serve as potential therapeutic targets for this disease.

Contents

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1. Introduction

Acute lung injury (ALI), a common and devastating respiratory disease, is characterized by trans-epithelial neutrophil migration, an uncontrolled inflammatory response, damage caused to lung epithelial and endothelial cells, and destruction of the associated cell barrier (1,2). According to the newer Berlin definition (3,4), the concept of 'acute lung injury' that was used for the milder form of acute respiratory distress syndrome (ARDS; the definition of ARDS/ALI is provided in Table I) (4,5) in the former definition has been discarded, although the term 'ALI' is still used for the milder form in the present review. Among the pathophysiological features of ALI, the destruction of lung vascular integrity is one of the most important, as this leads to the flow of protein-rich fluid into the alveoli, the accumulation of neutrophils in the pulmonary microvasculature, and the release of toxic mediators from activated neutrophils (e.g., proinflammatory cytokines and proteases) (2,6-8). ALI may be induced by direct causes (such as inhalation injury, serious pneumonia and drowning) or indirect causes (such as trauma, sepsis and drug overdose) (9). Clinically, ALI is mainly responsible for causing hypoxemia, pulmonary edema, bilateral lung infiltration and decreased lung compliance, which leads to the high morbidity and mortality rates observed in intensive care units (ICU) (10,11). Several biomarkers have been shown to be closely associated with the high morbidity and mortality rates that are due to ALI. To date, a number of studies have demonstrated that tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8 and IL-18 are the most closely associated with the outcome of ALI (12,13). In addition to these cytokines, alveolar epithelial biomarkers (including surfactant D and the receptor for advanced glycation end-products), protein C and plasminogen activator inhibitor-1 have been shown to be associated with the prognosis of the disease (14-16).

Although ALI continues to garner increasing levels of attention, few useful clinical therapeutic methods are available for the treatment of this disease. Lung-protective mechanical ventilation, the main clinical treatment method available, is used to improve the breathing condition of patients, thereby increasing their survival rate, although the mortality rate due to ALI/ARDS remains high (17,18). In addition, neither anti-inflammatory drugs (such as corticosteroids) nor β-adrenoceptor agonists have been demonstrated

to effectively reduce the mortality rate of patients with ALI (19,20). Table II (21-32) offers a summary of the research that has been conducted on the pharmacological treatment of ALI to date. Current research studies have indicated that stem cell-based therapies may potentially provide an important means of treating ALI due to their regenerative potential, stability and safety (33). Furthermore, microRNAs (miRNAs) have been shown to function as potential biomarkers, are a therapeutic target in animal models of ALI, and may ultimately serve as putative biopharmaceuticals based on studies that have been performed from the bench to the clinic (34,35). However, there remain limitations and issues that need to be explored and resolved. Essentially, it is necessary to further understand the mechanisms underlying the pathophysiological process of ALI, and to identify novel therapeutic approaches to improve the survival rate and prognosis of patients with ALI (36). As a dynamic organelle, the mitochondrion provides an important intracellular component that allows cells to adapt to the environment, also participating in stress sensing. The functions of mitochondria include bioenergetic, biosynthetic and signaling aspects (37). For example, mitochondria produce adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS). They also take up intracellular Ca^{2+} and relieve the effects of toxicity associated with reactive oxygen species (ROS) (38,39). Mitochondrial dysfunction usually results in cell death, and even tissue damage (Fig. 1). In addition, mitochondrial dynamics comprises one of the most critical features of mitochondrial biology, being crucially involved in the establishment and development of multiple types of lung disease (40). Mitochondrial dynamics is a quick and transient process involved in apoptosis, immunity, cellular signaling, and the cell cycle (41). This process comprises a coordinated cycle of fission and fusion of mitochondria that operates in order to maintain their intracellular shape, size and distribution, although this process differs according to the types of cells involved, and the underlying molecular mechanism is known to be associated with the pathogenesis of human diseases (42,43). Therefore, deciphering the underlying mechanisms of mitochondrial biology and mitophagy will help to strengthen our understanding of these processes, leading to the development of possible new treatments. To complete this review, the literature containing keywords such as 'mitochondria' and 'ALI' was searched in PubMed; most of the papers used were published in the last 5 years. The present review will consequently first provide an outline of the mitochondrial structure and the processes of mitochondrial biology and mitophagy, and subsequently will summarize the current state of play with research on the association of mitochondria with ALI, also discussing the role of mitochondria in ALI.

2. Structure and function of mitochondria

Mitochondria are double-membrane organelles that not only have complex and special structures, but also perform numerous functions. They exist in eukaryotic organisms and are located around the cellular nuclei (44). According to the current prevailing theory, it is considered that mitochondria were derived from bacteria that formed new symbiotic cells in combination with proto-eukaryotic cells, a fact that would explain how the structure of a mitochondrion is similar to that of a bacterium (45). A mitochondrion is composed of an inner membrane, an outer membrane, the intermembranous space, the aqueous spaces and the mitochondrial matrix (46,47). The mitochondrial outer membrane is permeable to molecules <5,000 Da in size that are able to enter the mitochondrion through the channel proteins (48), whereas the mitochondrial inner membrane is only minimally permeable to molecules and ions, and OXPHOS is localized to the inner membrane (49,50). Over 1,000 different types of protein reside in the spaces of the mitochondrion, including the protein complexes from eukaryotic organisms or bacteria, and approximately 500 of them are localized in the human mitochondrial matrix (51-53). In cells, most proteins are translated in the cytoplasm, and are subsequently transported into the mitochondria via the translocase of the outer membrane and the inner membrane (54,55). In addition to proteins, the mitochondrion contains its own genome in the mitochondrial DNA (mtDNA), which is a 16-kb circular molecule that encodes associated electron transport chain (ETC) proteins, rRNAs and tRNAs (56). The ETC comprises the enzyme complexes I-IV, cytochrome *c* and coenzyme Q (57) (Fig. 2). The status of mtDNA and the associated nuclear-encoded proteins exert an influence on the health, fertility and lifetime of organisms (58-61). Furthermore, the level of compatibility between mtDNA and nuclear genes has been shown to influence the genetic divergence (62,63). The main function of the mitochondrion is to produce ATP via OXPHOS, and to provide energy for the cells (64). Mitochondria can also function as a protein-protein signaling platform that helps to maintain the balance among several metabolic pathways, including the tricarboxylic acid cycle (58,65,66). Metabolites (ROS, cytochrome *c* and succinate) produced by mitochondria are essential for cellular signal transduction, and mitochondrion-associated signaling significantly contributes towards the maintenance of cellular and body health (67,68).

3. Pathophysiology of mitochondria

Mitochondrial dynamics. Mitochondrial dynamics refers to the reshaping, rebuilding and recycling process of mitochondria, which is mainly divided into mitochondrial fusion and mitochondrial fission (69). The mitochondrial fusion process mainly occurs in the early S and G1 phases of the cell cycle, in order to ensure the normal functioning of cellular respiration and ATP production for the synthesis of proteins (70). By contrast, the process of mitochondrial fusion ensures that material exchange in the mitochondrion and the removal of damaged intra-mitochondrial molecules can occur, which helps to repair defective mitochondria and further protect the mitochondrion from the process of engulfment during mitophagy in the cell (71,72). This fusion process includes the respective fusion events of both the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM) (73), and the sequence of events in the predominant molecular mechanism are as follows. First, trans-complexes of mitofusins are formed through dimerization of the transmembrane dynamin-like GTPases mitofusin 1 and mitofusin 2 (Mfn-1 and Mfn-2, respectively; the functions of these proteins are determined by their tissue-specific mRNA and protein expression), which is promoted via disulfide-bond

Table I. Definition of ARDS (4).

Parameters	Pathophysiological features
Timing of the onset	Within 1 week of a known clinical insult or new or worsening respiratory symptoms (most patients are identified within 72 h) (5)
Chest imaging (chest radiograph or computed tomography scan)	Bilateral opacities (cannot totally be explained by effusions, lobar/lung collapse, or nodules), more extensive opacities may be considered as more severe ARDS
Origin of edema	Respiratory failure cannot totally be explained by cardiac failure or fluid overload Requires objective evaluation (e.g., echocardiography) to exclude hydrostatic edema if no risk factor for ARDS is present
Oxygenation	
Mild	200 mm Hg $<PaO_2/FIO_2 \leq$300 mm Hg with PEEP or CPAP ≥5 cm H_2O (definition of 'acute lung injury' in this review)
Moderate	100 mm <Hg $PaO_2/FIO_2 \leq$200 mm Hg with PEEP ≥5 cm H_2O
Severe	$PaO_2/FIO_2 \leq$100 mm Hg with PEEP ≥5 cm H_2O

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Table II. Research on pharmacological treatment of acute lung injury.

Treatment	Results	(Refs.)
Glucocorticoids	No benefit (acute or late phase)	(21,22)
Surfactant	No benefit	(23)
N-acetylcysteine	No benefit	(24)
Inhaled nitric oxide	No benefit	(25)
Liposomal PGE 1	No benefit (low dose); Improved survival trend (high dose)	(26,27)
Ketoconazole	No benefit	(28)
Lisofylline	Terminated due to futility	(29)
Salbutamol IV	Improved survival trend	(30)
Procysteine	Terminated due to futility	(31)
Activated protein C	Terminated due to futility	(32)

formation, causing OMMs to come into proximity with each other and to be tethered, subsequently leading to fusion (74-77). Secondly, fusion of the IMM is then facilitated by OXPHOS, which accelerates the proteolytic action of the dynamin-associated GTPase optic atropy-1 (Opa-1), and this process cleaves long Opa-1 into a short and soluble form. Only the long Opa-1 (L-Opa-1) form is a component of the IMM, which facilitates fusion of the IMM (78,79). NM23-H4 is a type of nucleotide diphosphate kinase that promotes the GTP loading of Opa-1 in the presence of ATP (80). Opa-1 GTP loading/hydrolysis and S-S-proteolytic processing are two necessary steps in the process of IMM fusion (80). Opa-1 also has a key role in various mitochondria-associated cellular functions, such as participating in the respiratory chain and apoptosis (81). Thirdly, under conditions of metabolic stress, such as that which occurs during membrane potential dissipation, the metallopeptidase Oma-1 (an inner membrane ATP-independent protease) exerts its function via inducing Opa-1 to ultimately degrade into the short form of Opa-1 (S-Opa-1), which leads to damaged mitochondria being selected for mitophagy (82). Mitochondrial fission occurs mainly during the S-, G2- and M-phases of the cell cycle in order to ensure that the mitochondria are distributed equally in the daughter cells (83). Mitochondrial fission is a complex and multistep process that serves a crucial role in the regulatory mechanisms of cellular proliferation, differentiation, apoptosis, mitochondrial quality control and ROS production (84-87). For example, mitochondrial fission has been demonstrated to accelerate the segregation and autophagy of damaged mitochondria under stress conditions, which effectively reduces the accumulation of dysfunctional mitochondria and subsequently ameliorates the cellular stress conditions (88). The GTPase dynamin-related protein 1 (Drp1/DNM1L) is the primary driving factor of mitochondrial fission (89). The site of mitochondrial fission is marked by an initial constriction at the OMM that is generated by endoplasmic reticulum (ER) and actin filaments, which helps the recruitment of Drp1 at the fission site (90). In mammals,

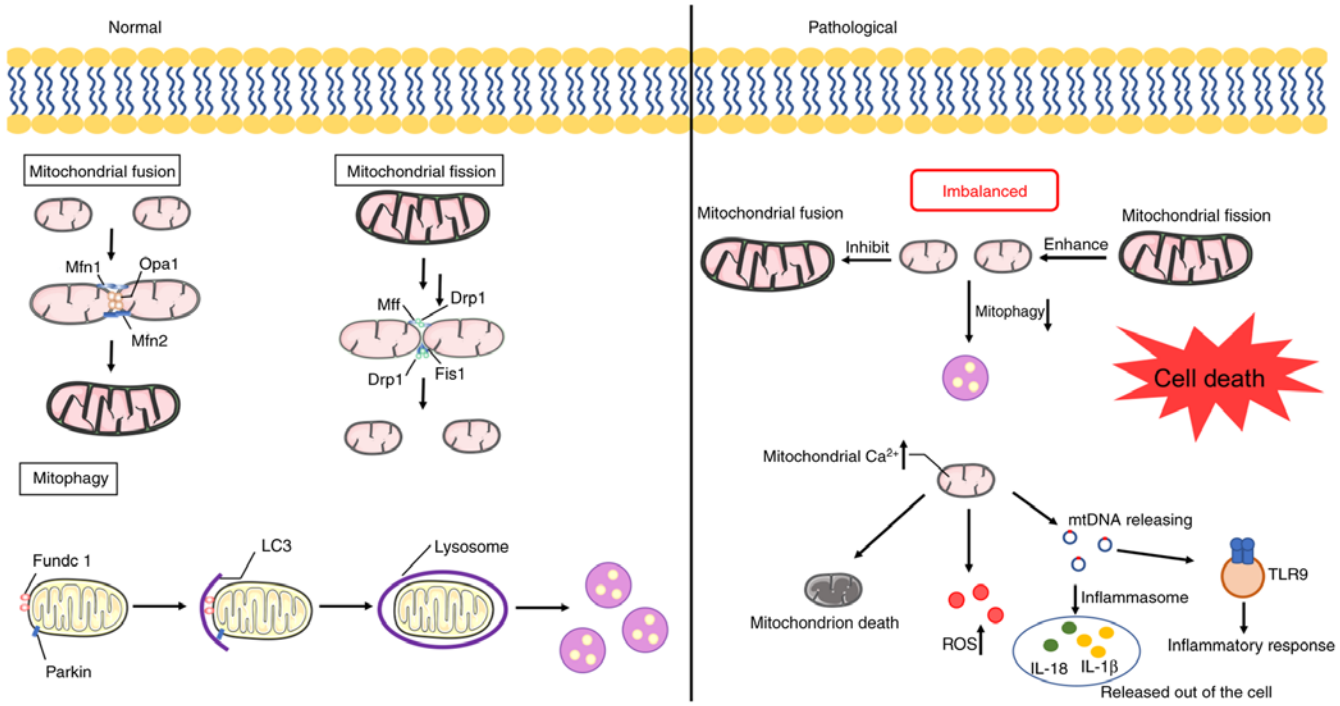

Figure 1. Pathophysiological processes of mitochondria in cells. Under normal conditions, the balance among mitochondrial fusion, mitochondrial fission and mitophagy maintains the health of mitochondria the number of mitochondria stable. The dysfunction of mitochondria usually occurs in the pathological conditions of cells, including the imbalance of mitochondrial dynamics, the release of Ca^{2+}, mtDNA and ROS from mitochondria, and the death of mitochondria. Mfn-1, mitofusin1; Mfn-2, mitofusin 2; Opa-1, optic atropy-1; Mff, mitochondrial fission factor; Drp1, dynamin-related protein 1; Fis 1, mitochondrial fission 1; LC3, microtubule-associated protein 1 light chain 3; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; TLR, Toll-like receptor; IL, interleukin.

although Drp1 is unable to bind to the phospholipid membrane directly due to the loss of a pleckstrin homology (PH) domain, Drp1 is nevertheless able to exert this function via adaptor proteins [mitochondrial fission factor (Mff) and mitochondrial dynamics proteins 51 and 49 (MiD51 and MiD49)] (91-93). Mitochondrial scission mainly occurs at the site of ER contact, suggesting that both phospholipids [predominantly phosphatidic acid (PA) and cardiolipin (CL)] and calcium transfer are indispensable during this scission process (94,95). Dynamin 2 (Dnm-2; a GTPase) is recruited at the contact site, where Drp1 recruits and induces the membrane constriction, finally leading to mitochondrial fission (30). There also exists another mechanism of IMM fission which is dependent on calcium instead of Drp1. When inverted formin 2 (INF2) proteins are recruited at the contact site, more INF-2-mediated calcium enters into the mitochondria, which leads to a decrease in the membrane potential, the cleavage of Opa-1, and the activation of Oma-1 (96). S-Opa-1 is an important component of the mitochondrial contact site and the intermembrane space bridging (MIB) complex. It controls the OMM-IMM tethering mediated by Mic60, promotes the release of IMM tethering and possible shrinkage, and ultimately regulates the mitochondrial inner compartment (CoMIC) (97). S-Opa-1 participates in the procedure of cristae morphogenesis and the tethering of the OMM along with other associated proteins, such as mitofilin (Mic60/Immt), ChchD3, ChchD6 and Sam50 (a type of outer membrane protein) (97,98). In addition, there exists other mitochondrial-fission regulatory proteins, including the leucine-rich repeat kinase 2 (LRRK2) and the small GTPase, Rab32 (99,100).

Mitophagy. Mitophagy clears damaged or dysfunctional mitochondria to control the mitochondrial quality, and the dysregulation of mitophagy is associated with a number of different diseases (101). There are both canonical and non-canonical modes that mediate the signaling pathway in mitophagy. Mitophagy induced by PTEN-induced putative kinase 1 (PINK1) and Parkin is the most common mechanism, which is a multistep process of degrading unhealthy mitochondria via the activation of PINK1, Parkin and other recruited proteins (102-104). In a normal cellular environment, PINK1 protein at the OMM is constitutively cleaved and degraded by mitochondrial processing protease (MPP) and presenilin-associated rhomboid-like (PARL) protein. When the mitochondrial membrane potential is perturbed, and subsequently the mitochondrial membrane is depolarized, PINK1 is stabilized at the OMM since both MPP and PARL are inhibited, which could be considered as the signal of mitochondrial dysfunction (105). PINK1 is activated via its autophosphorylation, which further leads to the phosphorylation of its substrates. PINK1 phosphorylates serine-65 of ubiquitin to activate and recruit Parkin, which serves to amplify the PINK1-initiated signal. Subsequently, activated Parkin induces the ubiquitinylation of mitochondrial fusion-associated proteins such as Mfn-1 and Mfn-2, which serves to prevent them from participating in the fusion process (106,107). The ubiquitinylation of Miro1 protein induced by Parkin weakens the protein ability of Miro1 to bind with microtubules, and strengthens the ability of this protein to bind with the PINK1-Parkin complex, which causes the isolation of associated damaged mitochondria (108). Concurrently, the phosphorylation of the ubiquitin chain mediated by PINK1 enhances the recruitment and

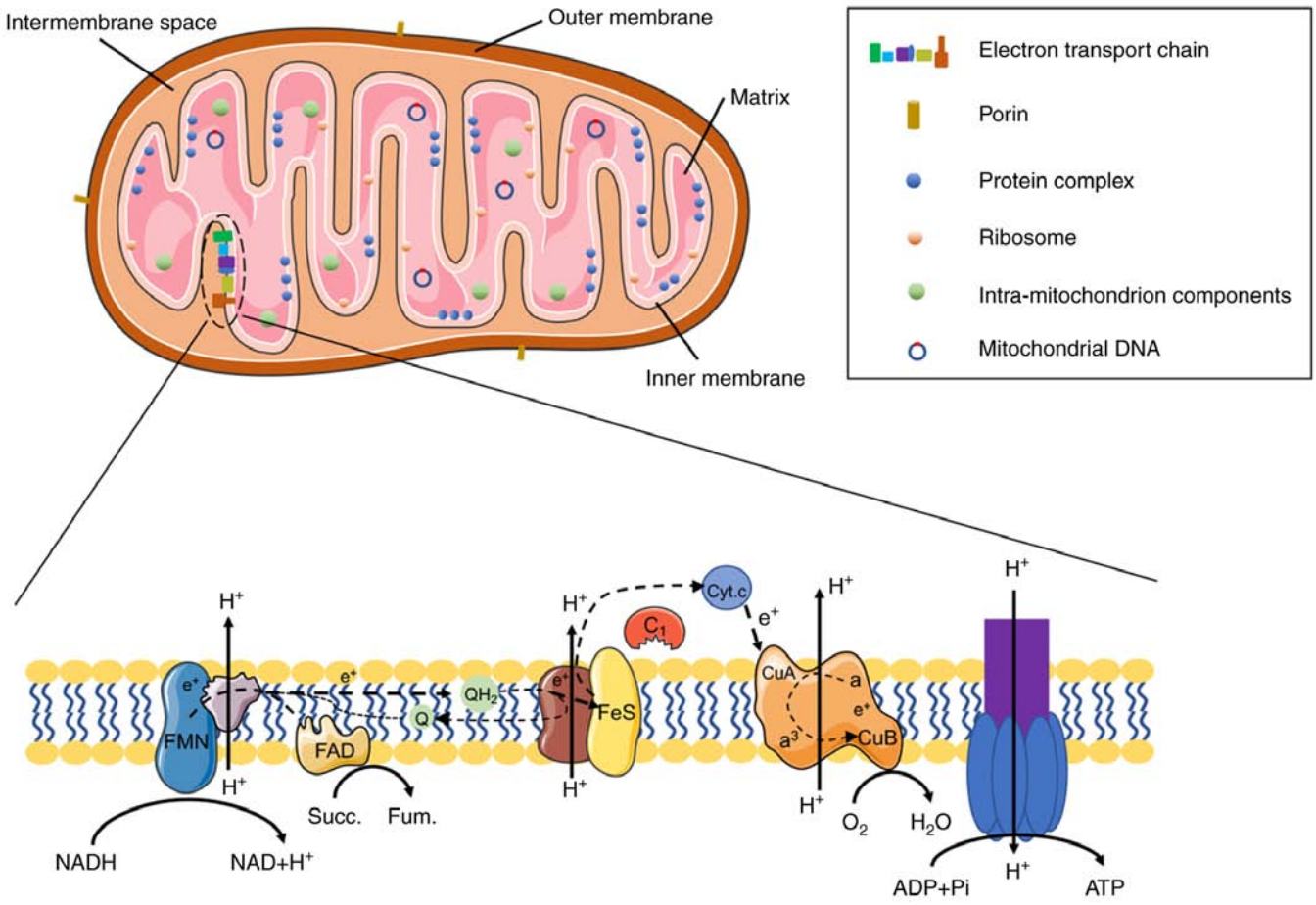

Figure 2. Structure of mitochondria and electron transport chain. Mitochondria are organelles having an outer and inner membrane. The components of citric acid cycle, mtDNA, protein complexes and ribosomes are all in the inside of the inner membrane. The respiratory chain proteins are located on the inner membrane. There are five components of the electron transport chain, including NADH/ubiquinone oxidoreductase, succinate dehydrogenase, cytochrome *c* reductase, cytochrome *c* oxidase, and mitochondrial ATP synthase. The energy stored by proton pumping is utilized by the electron transport chain to phosphorylate ADP to ATP. FMN, flavin mononucleotide; NAD, nicotinamide adenine dinucleotide; NADH, ubiquinone oxidoreductase; Succ., Succinate; Fum., Fumarate; FAD, flavin adenine dinucleotide; Cyt c, cytochrome *c*; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

activation of Parkin. Microtubule-associated protein 1 light chain 3 (LC3) on the autophagosome directly interacts with polyubiquitinylated proteins recognized by cargo adaptors, leading finally to the formation of a complex that is degraded by autophagy (109).

In other canonical mechanisms, both Bcl-2 homology 3 (BH3)-only protein (Nix, also known as Bnip3L) and BCL-2/adenovirus E1-interacting protein 3 (Bnip3) not only interact with LC3, but also exert their function under the regulation of hypoxia-associated factors, which serves an important role in mitophagy (110,111). FUN14 domain-containing 1 (FUNDC1), an OMM protein, is also associated with mitophagy through its interaction with LC3, Opa-1 and Drp1 (112,113).

In addition, there are a variety of non-canonical mitophagy pathways. Depolarized mitochondrial CL is able to directly interact with GABAA receptor-associated protein (Gabarap) in the OMM, and the oxidation status of CL serves to regulate the balance between cytoprotective mitophagy and other mitochondrial death pathways (114). Prohibitin 2, a receptor present in the IMM, is able to promote Parkin-mediated mitophagy through interacting with LC3 (115). Furthermore, Beclin-1 regulator 1 (AMBRA1) and Bcl-2-like protein 13 (BCL-2L13), as mitophagy receptors, have been shown to induce and promote mitophagy (116,117). BCL-2L13 is also involved in Parkin-independent mitophagy (118).

Considering all the evidence, it has been clearly demonstrated that dysfunction of mitophagy leads to the accumulation of damaged mitochondria, which induces oxidative stress and various pathological states.

Dysfunction of the ETC. With the ETC (also called the respiratory chain), a liberation of electrons results from the oxidation of NADH and $FADH_2$. The liberated electrons are passed along the carrier complexes, and eventually transferred to an oxygen molecule (119). ROS derived from mitochondrial superoxide are mainly produced by Complex I/III of the ETC in mitochondria (120). Heightened ROS production is induced by infection, inflammation, air pollution and oxidative stress, supporting the notion that ALI may lead to the high levels of ROS that are observed (121). Low concentrations of ROS and superoxide (such as peroxynitrite and hydrogen peroxide) are considered to be important components of a normally functioning cellular signaling pathway, whereas high levels of these molecules are able to induce ETC damage under pathological conditions (122). As one of the underlying causes of ALI, sepsis

also has an impact on the function of the ETC. It has been demonstrated that the level of mitochondrial ROS increases in numerous organs, which results in abnormalities of the ETC in the same organs, as observed in cases of sepsis (123,124). It has been shown that the concentrations of ETC proteins that are associated with or contain iron-sulfur centers are reduced in sepsis, since Fenton reactions induce the depletion of ETC protein constituents (125). When the mitochondrial ETC components are damaged or even lost in cases of severe disease, the decreased production of ATP may accelerate the pathological processes of certain diseases (126-128).

Free radical production. In addition to the direct damage caused to ETC proteins, an abnormal expression of ROS derived from mitochondria may influence other cellular constituents, and the interactions between ROS and these constituents subsequently alter their function; this includes proteins, DNA, and lipid peroxidation (129,130). Since mtDNA lacks protective histones and the expression of bases modified by oxidation in mtDNA is several times higher compared with that in nuclear DNA, mtDNA is more easily impaired by ROS (131,132). It has been shown that superoxide anions produced by mitochondria have a limited ability to directly pass through the mitochondrial membranes, although they exit the mitochondrion more easily by forming new molecular species and reacting with cellular components in the cytoplasm (133,134). For example, under conditions in which the generation of nitric oxide significantly increases, nitric oxide may combine with superoxide forming peroxynitrite, which is able to impair proteins and modify lipids (135). Moreover, ROS oxidize proteins and alter their activity, promoting the release of proteases and inhibiting the activation of antioxidant enzymes (136). In ALI, the overproduction of ROS is widely derived from parenchymal cells, a high concentration of oxygen and oxidant-generating enzymes, leading to the induction of oxidative stress and cell damage (137,138).

Abnormal mitochondrial Ca^{2+} transport. In quiescent cells, excess Ca^{2+} in the cytoplasm is taken up into mitochondria to maintain the low levels of cytosolic Ca^{2+} (139). There are several factors that influence the level of mitochondrial Ca^{2+}, including cytosolic Ca^{2+} that is released from other cellular organelles. During the process of mitochondrial Ca^{2+} transport, Ca^{2+} influx is dependent on calcium uniporter activity, and to a certain extent the Ca^{2+} that is released is dependent on the mitochondrial sodium/calcium ion channel (140,141). Under conditions of there being an increased level of cytosolic Ca^{2+} and an increased level of activity of the uniporter, ATP synthase is likewise activated, and the levels of mitochondrial calcium are increased (142). Extremely high concentrations of mitochondrial Ca^{2+} may lead to increases in the formation of mitochondrial superoxide and ROS, which cause mitochondrial-dependent cellular damage (143). Furthermore, the increased levels of mitochondrial Ca^{2+} are coordinated with enhanced mitochondrial ROS to induce opening of the membrane permeability transition (MPT) pore, which results in cytochrome *c* being released from mitochondria, subsequently activating the mitochondrial-dependent cell death pathway (144). It has been reported that hypocapnia-induced mitochondrial Ca^{2+} uptake could increase the production of ROS, which ultimately results in the cell death associated with ARDS (145).

4. Mitochondrial role in ALI

Mitochondrial dysfunction in lung cells has an important role in the pathological process of ALI (146). The main pathological feature of ALI is the infiltration of inflammatory cells, such as macrophages and neutrophils (147,148). Mitochondria are involved in the modulation of immune cells via different mechanisms. It has been demonstrated that mitochondrial ROS can stimulate the activation of macrophage-surface Toll-like receptors (TLRs), enhancing their anti-pathogenic ability (149). Triggering receptor expressed on myeloid cells 1 (TREM-1) maintains the integrity of mitochondria to prolong the survival of macrophages which plays a key role in ALI (150). Moreover, macrophages can be divided into two phenotypes, M1 (proinflammatory) and M2 (anti-inflammatory) respectively, which are associated with the bioenergetic function of mitochondria and are an essential part in the process of lung infection and inflammation (151,152). The mitochondrial ETC is involved in the activation of lipopolysaccharide (LPS)-induced nuclear factor-κB (NF-κB), suggesting that mitochondria alleviate the degree of damage of ALI by regulating neutrophils (153).

LPS is known to damage alveolar epithelial cells and is one of the main causes of ALI. Islam *et al* found that mitochondria derived from bone marrow-derived stromal cells were released in the microvesicles engulfed by the alveolar cells, which increased the concentration of alveolar ATP and decreased the mortality of animal models in LPS-induced ALI (154). In current research, the heme oxygenase-1/carbon monoxide system has been revealed to alleviate ALI induced by endotoxin via regulating the mitochondrial dynamic equilibrium (155,156). In LPS-induced ALI rat models, the expression of Mfn-1 is negatively regulated by HO-1 expression possibly related to the PI3K/Akt signaling pathway, which can improve the condition of oxidative stress by regulating mitochondrial fusion (157). The mitochondrial division inhibitor-1 (Mdivi-1) has the ability to relieve the activation of mitogen-activated protein kinases (MAPKs), oxidative stress and apoptosis induced by LPS and reduce pro-inflammatory cytokine release, which inhibits the mitochondrial fission and mitigates the degree of damage by ALI (158). In LPS-induced ALI, the severity of inflammation and lung injury can be restrained by regulating the Drp1-induced mitochondrial fission (159). Dexmedetomidine (DEX) affords lung protection and mitigates the damage of ALI by keeping the dynamic balance between mitochondrial fusion and fission via the HIF-1a/HO-1 pathway (160). Normal mitophagy maintains the homeostasis of cells by cleaving and degrading damaged mitochondria, while excessive mitophagy may lead to mitochondrial dysfunction, cell damage and death. Sestrin2 (Sesn2), a highly conserved protein, protects alveolar macrophages and reduces the release of the Nod-like receptor protein 3 (NLRP3) inflammasome by promoting mitophagy, which finally plays a protective role in LPS-induced ALI (161). Transcription factor EB (TFEB) negatively regulates mitophagy and decreases mitochondrial injury to protect LPS-induced ALI (162,163). Overexpression

of PPARγ coactivator 1α (PGC-1α) may positively regulate the expression of TFEB and then affect mitophagy, which in turn alleviates lung edema and decreases inflammation in LPS-induced ALI (164). Zhao *et al* demonstrated that oxyberberine inhibited the translation of Parkin1 from the cytoplasm to mitochondria and Parkin-mediated mitophagy to ease the degree of inflammation in LPS-induced ALI (165). Moreover, overexpression of Bcl-2 proteins also attenuated LPS-induced ALI via PINK1/Parkin-mediated mitophagy (166).

The lungs are one of the organs most often affected by sepsis, which usually leads to ALI. Damage-associated molecular pattern (DAMP) is the general term for numerous endogenous risk molecules, existing in the nucleus, mitochondria, or cytoplasm (167,168), which are released in response to cell death or stress (169,170). The released DAMPs are recognized and bond to multiple receptors which include pattern recognition receptors (PRRs), and then activate downstream pathways to trigger the inflammatory response, aggravating the damage of the lungs (171,172). mtDNA, a type of cellular toxicity compound, acts as a DAMP and contains materials only found in bacteria and induces cellular toxicity via two main mechanisms (173,174). The first one is to activate and interact with NLRP3 inflammasome, and the second one is to recognize the bacteria-like mtDNA via the activation of TLR9 (175,176). For example, the release of mtDNA depends on the level of TLR4, and mtDNA induces ALI together with TLR9 (177). In addition, mtDNAs, as mitochondrial DAMPs, increase the permeability of lung endothelial cells in sepsis-induced ALI (178). The balance between mitochondrial fusion and fission is broken when massive ROS exist, which accelerate the progression of sepsis and are an indirect cause of ALI (179). Chen *et al* found that PINK1/Parkin-mediated mitophagy played a protective role in cecal ligation and puncture (CLP)-induced ALI (180). It has been proven that Nrf2 regulates mitophagy in lung cells and exerts a protective function in sepsis (181). MAP kinase kinase 3 (MKK3) promotes the activation of mitochondrial biogenesis and mitophagy through the PINK1/Parkin pathway and PGC-1α/Nrf-1 axis, which in turn increase the number of healthy mitochondria and protect against sepsis-induced ALI (182).

Reportedly, hydrochloric acid-induced ALI may result in the direct damage of the alveolar epithelium and then induce proinflammatory signaling (183,184). However, the pathophysiological mechanisms of hydrochloric acid-induced ALI are still not clear. Hough *et al* found the mitochondrial function of alveolar cells impaired in hydrochloric acid-induced ALI (185). Acute PM2.5 exposure was related to enhanced airway inflammation, immune cell infiltration, and the release of proinflammatory cytokines and chemokines, inducing ALI (186,187). The activation of the TLR4/NF-κB/p38 MAPK and NLRP3/caspase-1 signaling pathways may inhibit ALI and mitochondrial damage by regulating the expression of the related mitochondrial fusion and fission proteins, such as Opa-1, Drp1, and Mfn-2 (188). Ischemia/reperfusion injury (IRI) usually includes the release of cytokines and inflammatory mediators, extensive oxidative stress, and the induction of apoptosis, increasing the dysfunction and damage of lungs (189). Tanshinone IIA (TIIA) combined with cyclosporine A (CsA) attenuated the apoptosis of the lung tissue by improving the mitochondrial dynamics via the PI3K/Akt/Bad signaling pathway (190). Prolonged, high oxygen concentration promoted the production of ROS and the level of proapoptotic proteins, finally inducing ALI. Research has shown that thyroid hormone T3 increases mitochondrial biogenesis and mitophagy, thus providing effective protection in hyperoxia-induced ALI (191).

In summary, the dysfunction of mitochondria plays a crucial role in ALI. These findings suggest the potential of mitochondrial biology and mitophagy as targets for the treatment and intervention of ALI.

5. Current therapies and potential regulatory factors

Mitochondria play an indispensable role in the occurrence and development of ALI. In addition, in ALI models, cells undergo abnormal mitochondrial biological processes or mitophagy. Thus, factors associated with mitochondrial pathophysiology may be the potential therapeutic targets for ALI (Fig. 3) (192). Mitochondrial-targeted antioxidants can protect against the mitochondrial dysfunction and oxidative stress induced by mechanical ventilation, suggesting improvement of the prognosis of ALI treated by mechanical ventilation (193). Research has also demonstrated that both pioglitazone and rosiglitazone effectively induce mitochondrial biogenesis and prevent the related cell dysfunction and damage (194). Mitochondrial transplantation, as an important method to replace damaged mitochondria, can significantly improve the condition of lungs and reduce the lung tissue damage induced by ALI (195). Melatonin can effectively inhibit superoxide and nitric oxide and protect against the mitochondrial damage (196-198).

In addition to current therapies, there are also certain factors that regulate mitochondrial dynamics, which may aid in understanding the role of mitochondria in ALI and may be translated into novel therapies in the future. Membrane lipid composition and post-translation modification are two main factors that regulate mitochondrial dynamics. CL and PA are two minor constituents of phospholipids, but they are both involved in the remodeling of the mitochondrial membrane. PA, a saturated lipid synthesized in the endoplasmic reticulum (ER), is transferred from the ER to the mitochondria and then converted into CL at the inner mitochondrial membrane (199). The respective microdomain formation of PA and CL determines mitochondrial fusion or fission (200-202). It has been shown that Drp1 can interact with these two phospholipids to influence mitochondrial fusion or fission (200, 203-205). Drp1 is the core protein of mitochondrial dynamics, and how post-translational modifications of Drp1 regulate mitochondrial dynamics has been widely explored (206-208). In addition to membrane lipid composition and post-translation modification, there are also other proteins that modulate this dynamic process, including ganglioside-induced differentiation associated protein 1 (GDAP1) (209), mitochondrial fission process 1 (MTFP1/MTP18) (210), and reactive oxygen species modulator 1 (ROMO1) (211).

To sum up, there is still a long way to go before these therapies and regulatory factors can be formally used in the clinic, because some of these potential treatments are still speculative and others have only been verified in animal models.

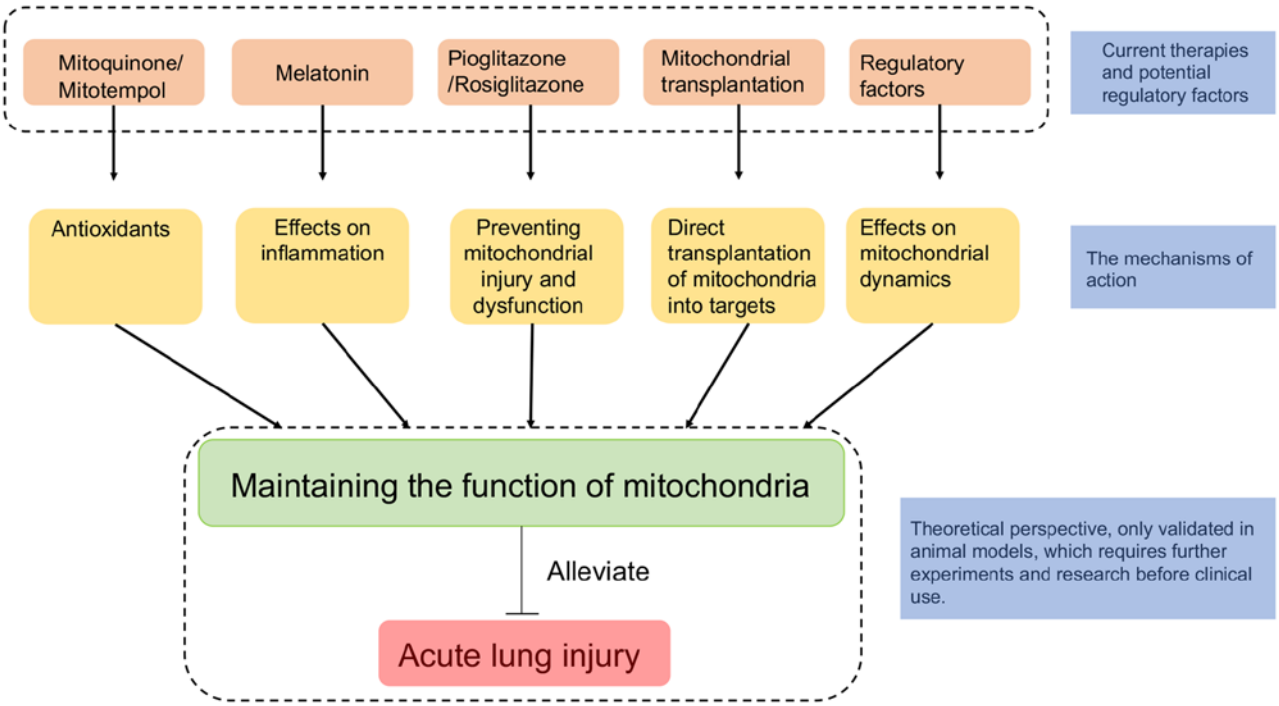

Figure 3. Schematic representation of potential mechanisms of current therapies and regulatory factors attenuating acute lung injury by the modulation of mitochondria. Mitochondria play important roles in acute lung injury, therefore factors protecting mitochondria may aid in improving the prognosis of acute lung injury.

6. Conclusion

The present review summarized the structure, function, pathophysiology of mitochondria and the role of mitochondria in ALI, which could pave the way to provide novel therapeutic methods to treat ALI.

ALI is a complex and severe pathological disease with high morbidity and mortality in the ICU, which triggers the sustaining inflammatory response, lung epithelial and endothelial cell death, and alveolar barrier destruction (212). Mitochondria are considered to be the powerhouse of cells, take part in metabolite biosynthesis and produce ROS (213). They have also been proven to be involved in necrosis, immunological response, thermoregulation, and intracellular calcium regulation (214,215). Generally, the dysfunction of mitochondria usually occurs in the pathophysiological processes of diseases.

Mitochondria play an important role in ALI. Macrophages and neutrophils are essential effector cells that are involved in ALI, and mitochondria regulate the polarization of macrophages and the apoptosis and NETosis of neutrophils (216,217). In addition, mitochondrial dynamics and mitophagy are associated with the outcome of ALI. Collectively, mtDNA, as a DAMP, induces ALI, and ROS produced by mitochondria affect the process and outcome of ALI.

However, there are some remaining issues that need to be addressed. The research on mitochondria-related elements in ALI is still in its infancy, and the changes in mitochondria and regulatory factors are complex and interactive. Moreover, the research concerning the role of mitochondria in ALI is based on animal models, warranting more experiments, in order to be brought into clinical practice.

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Authors' contributions

BZ and JS conceived and designed the review, collected and analyzed the data, and co-wrote the manuscript. JS reviewed the manuscript. Data authentication is not applicable. Both authors (BZ and JS) read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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