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

BIAO ZHAN[1-3] and JIE SHEN[1-3]

[1]Center of Emergency and Critical Medicine, Jinshan Hospital of Fudan University; [2]Research Center for Chemical Injury, Emergency and Critical Medicine of Fudan University; [3]Key Laboratory of Chemical Injury, Emergency and Critical Medicine of Shanghai Municipal Health Commission, Shanghai 201508, P.R. China

Received March 3, 2022; Accepted May 16, 2022

DOI: 10.3892/etm.2022.11406

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

1. Introduction
2. Structure and function of mitochondria
3. Pathophysiology of mitochondria
4. Mitochondrial role in ALI
5. Current therapies and potential regulatory factors
6. Conclusion

Correspondence to: Dr Jie Shen, Center of Emergency and Critical Medicine, Jinshan Hospital of Fudan University, 1508 Longhang Road, Shanghai 201508, P.R. China
E-mail: j1999sh@163.com

Key words: acute lung injury, acute respiratory distress syndrome, mitochondria, mitochondrial dysfunction, therapy

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 ≤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 ≤200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤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,

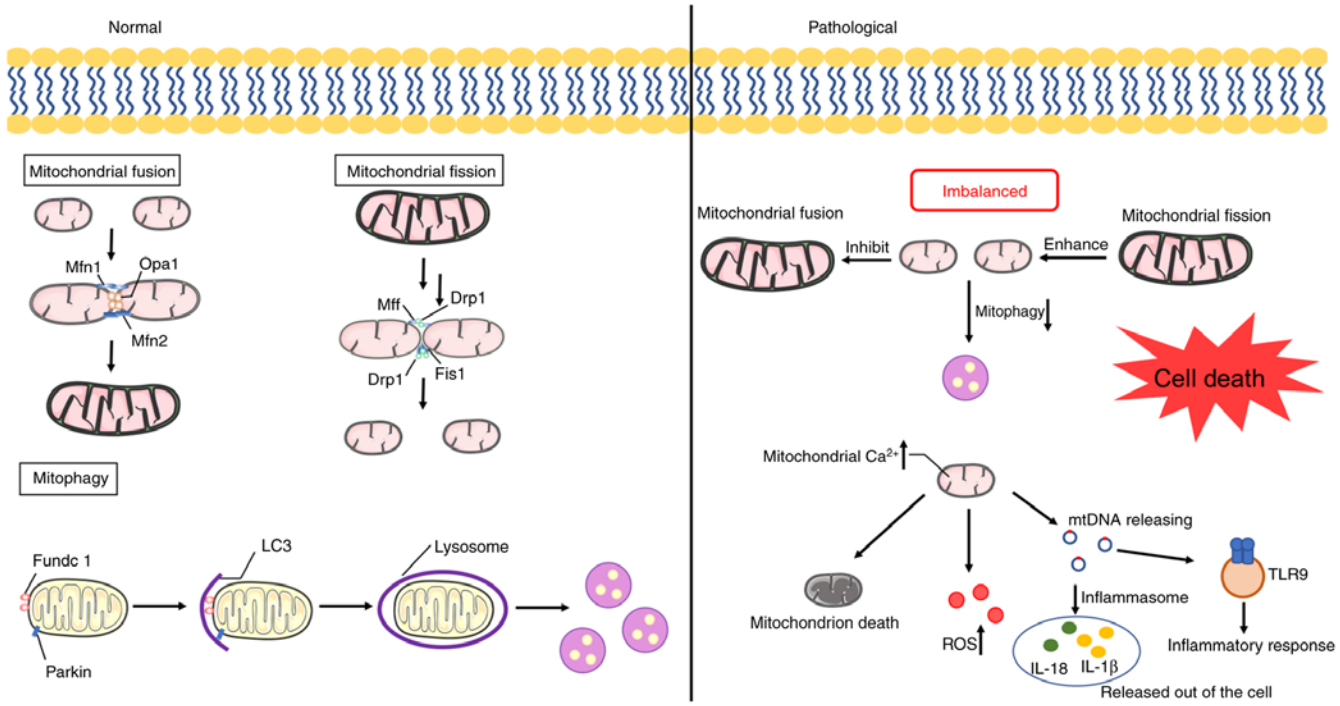

Figure 1. Pathophysiological processes of mitochondria in cells. Under normal conditions, the balance among mitochondrial fusion, mitochondrial fission and mitophagy maintains the health of mitochondria the number of mitochondria stable. The dysfunction of mitochondria usually occurs in the pathological 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

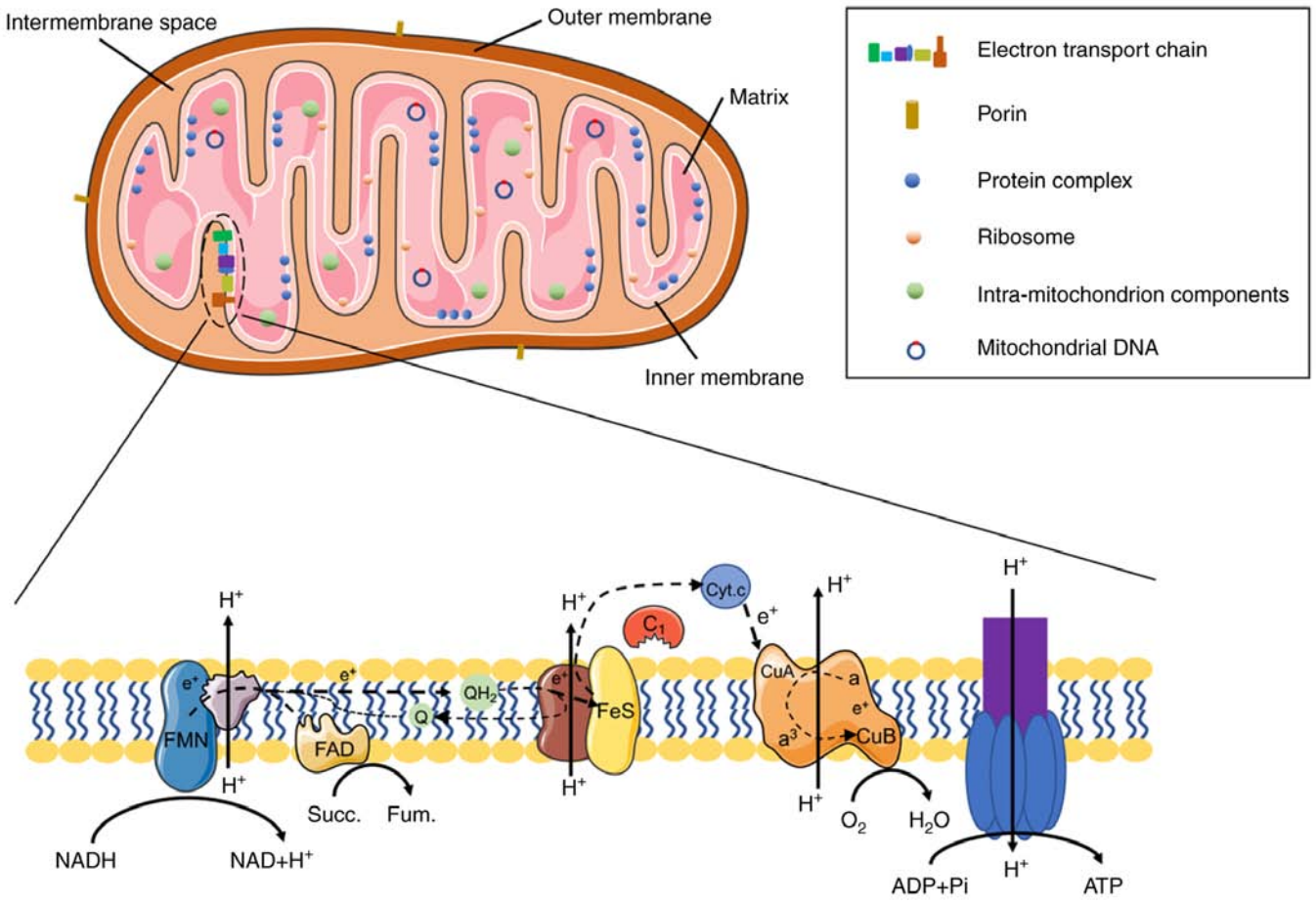

Figure 2. Structure of mitochondria and electron transport chain. Mitochondria are organelles having an outer and inner membrane. The components of citric acid cycle, mtDNA, protein complexes and ribosomes are all in the inside of the inner membrane. The respiratory chain proteins are located on the 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.

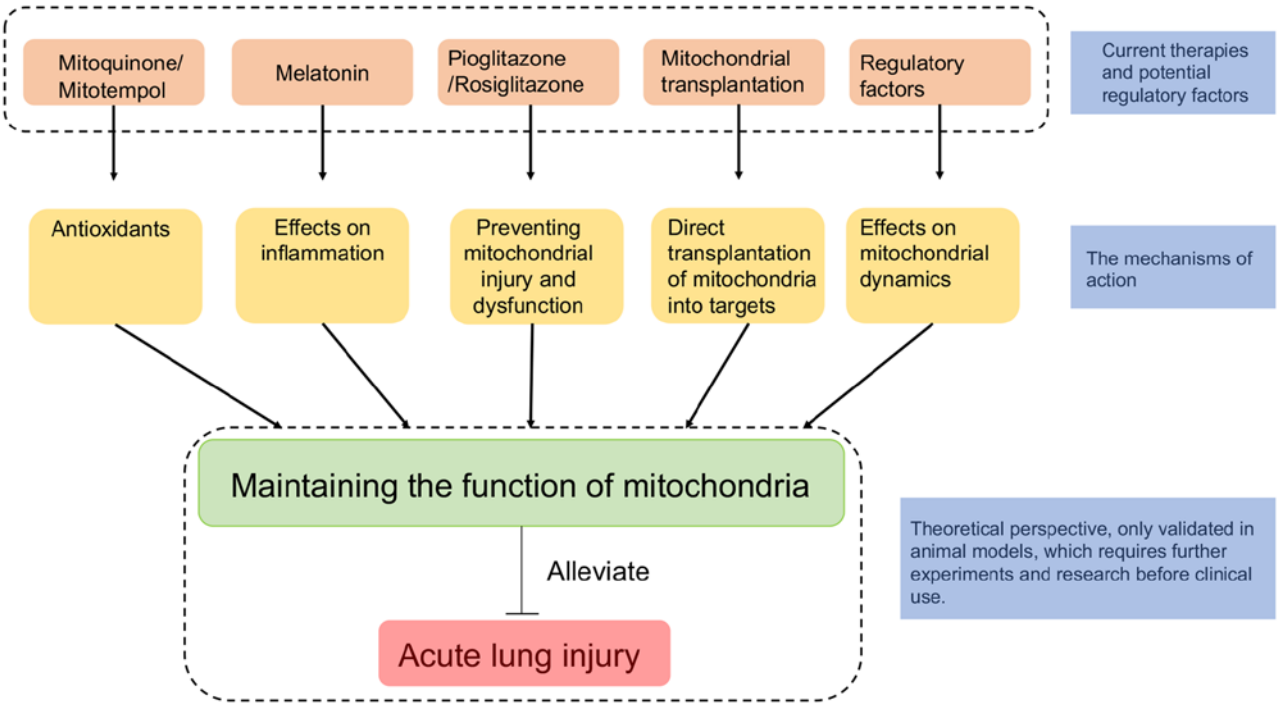

Figure 3. Schematic representation of potential mechanisms of current therapies and regulatory factors attenuating acute lung injury by the modulation of mitochondria. Mitochondria play important roles in acute lung injury, therefore factors protecting mitochondria may aid in improving the prognosis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

Acknowledgements

Not applicable.

Funding

The present review was supported by the Mass Chemical Injury First-Aid, Core Discipline Improvement Project, 3-year (2020-2022) Action Plan of Shanghai Public Health System Development (program no. GWV-10.1-XK26; budget no. 1304), the Emergency and Critical Care Centre, Discipline Platform Improvement Project, 3-year Talents Echelon Action Plan of Jinshan Hospital (program no. XPT-2020-3; budget no. 1257), and the Emergency and Critical Care, Class A, Core Medicine Discipline Improvement Project of Jinshan District, 6th Season (program no. JSZK2019A01; budget no. 1195).

Availability of data and materials

Not applicable.

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.

References

1. Jiang Z, Zhang L and Shen J: MicroRNA: Potential biomarker and target of therapy in acute lung injury. Hum Exp Toxicol 39: 1429-1442, 2020.
2. Mowery NT, Terzian WTH and Nelson AC: Acute lung injury. Curr Probl Surg 57: 100777, 2020.
3. Bernard G, Artigas A, Brigham K, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A and Spragg R: Report of the American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes and clinical trial coordination. The consensus committee. Intensive Care Med 20: 225-232, 1994.
4. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L and Slutsky AS: Acute respiratory distress syndrome: The Berlin definition. JAMA 307: 2526-2533, 2012.
5. Hudson LD, Milberg JA, Anardi D and Maunder RJ: Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151: 293-301, 1995.
6. Looney MR, Su X, Van Ziffle JA, Lowell CA and Matthay MA: Neutrophils and their Fc gamma receptors are essential in a mouse model of transfusion-related acute lung injury. J Clin Invest 116: 1615-1623, 2006.
7. Martin T, Hagimoto N, Nakamura M and Matute-Bello G: Apoptosis and epithelial injury in the lungs. Proc Am Thorac Soc 2: 214-220, 2005.
8. Weiser M, Pechet T, Williams J, Ma M, Frenette PS, Moore FD, Kobzik L, Hines RO, Wagner DD, Carroll MC and Hechtman HB: Experimental murine acid aspiration injury is mediated by neutrophils and the alternative complement pathway. J Appl Physiol (1985) 83: 1090-1095, 1997.
9. Spadaro S, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, Ragazzi R, Ruggeri P, Hansel TT, Caramori G and Volta CA: Biomarkers for acute respiratory distress syndrome and prospects for personalised medicine. J Inflamm (Lond) 16: 1, 2019.
10. Huang X, Xiu H, Zhang S and Zhang G: The role of macrophages in the pathogenesis of ALI/ARDS. Mediators Inflamm 2018: 1264913, 2018.
11. Han S and Mallampalli RK: The acute respiratory distress syndrome: From mechanism to translation. J Immunol 194: 855-860, 2015.
12. Meduri G, Kohler G, Headley S, Tolley E, Stentz F and Postlethwaite A: Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest 108: 1303-1314, 1995.
13. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR and Wheeler AP; NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network: Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 33: 1-6, 230-232, 2005.
14. Greene KE, Wright JR, Steinberg KP, Ruzinski JT, Caldwell E, Wong WB, Hull W, Whitsett JA, Akino T, Kuroki Y, *et al*: Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 160: 1843-1850, 1999.
15. Terpstra ML, Aman J, van Nieuw Amerongen GP and Groeneveld AB: Plasma biomarkers for acute respiratory distress syndrome: A systematic review and meta-analysis*. Crit Care Med 42: 691-700, 2014.
16. Ware LB, Matthay MA, Parsons PE, Thompson BT, Januzzi JL and Eisner MD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network: Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. Crit Care Med 35: 1821-1828, 2007.
17. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, *et al*: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315: 788-800, 2016.
18. Fan E, Brodie D and Slutsky AS: Acute respiratory distress syndrome: Advances in diagnosis and treatment. JAMA 319: 698-710, 2018.
19. Peter JV, John P, Graham PL, Moran JL, George IA and Bersten A: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. BMJ 336: 1006-1009, 2008.
20. McAuley DF and Matthay MA: Is there a role for beta-adrenoceptor agonists in the management of acute lung injury and the acute respiratory distress syndrome? Treat Respir Med 4: 297-307, 2005.
21. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA, *et al*: High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317: 1565-1570, 1987.
22. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT and Ancukiewicz M; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354: 1671-1684, 2006.
23. Doig C: Aerosolized surfactant in sepsis-induced adult respiratory distress syndrome. JAMA 273: 1259-1260, 1995.
24. Domenighetti G, Suter PM, Schaller MD, Ritz R and Perret C: Treatment with N-acetylcysteine during acute respiratory distress syndrome: A randomized, double-blind, placebo-controlled clinical study. J Crit Care 12: 177-182, 1997.
25. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K Jr, Hyers TM and Papadakos P: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Inhaled nitric oxide in ARDS study group. Crit Care Med 26: 15-23, 1998.
26. Vincent JL, Brase R, Santman F, Suter PM, McLuckie A, Dhainaut JF, Park Y and Karmel J: A multi-centre, double-blind, placebo-controlled study of liposomal prostaglandin E1 (TLC C-53) in patients with acute respiratory distress syndrome. Intensive Care Med 27: 1578-1583, 2001.
27. Abraham E, Carmody A, Shenkar R and Arcaroli J: Neutrophils as early immunologic effectors in hemorrhage- or endotoxemia-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 279: L1137-L1145, 2000.
28. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. The ARDS network. JAMA 283: 1995-2002, 2000.
29. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. Crit Care Med 30: 1-6, 2002.
30. Perkins GD, Gates S, Park D, Gao F, Knox C, Holloway B, McAuley DF, Ryan J, Marzouk J, Cooke MW, *et al*: The beta agonist lung injury trial prevention. A randomized controlled trial. Am J Respir Crit Care Med 189: 674-683, 2014.
31. Morris PE, Papadakos P, Russell JA, Wunderink R, Schuster DP, Truwit JD, Vincent JL and Bernard GR: A double-blind placebo-controlled study to evaluate the safety and efficacy of L-2-oxothiazolidine-4-carboxylic acid in the treatment of patients with acute respiratory distress syndrome. Crit Care Med 36: 782-788, 2008.
32. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, Tidswell M, Siegel MD, Soto G, Peterson MW, *et al*: Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med 178: 618-623, 2008.
33. Murphy MB, Moncivais K and Caplan AI: Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. Exp Mol Med 45: e54, 2013.
34. Rajasekaran S, Pattarayan D, Rajaguru P, Sudhakar Gandhi P and Thimmulappa RK: MicroRNA regulation of acute lung injury and acute respiratory distress syndrome. J Cell Physiol 231: 2097-2106, 2016.
35. Chakraborty C, Sharma AR, Sharma G, Doss CGP and Lee SS: Therapeutic miRNA and siRNA: Moving from bench to clinic as next generation medicine. Mol Ther Nucleic Acids 8: 132-143, 2017.
36. Johnson ER and Matthay MA: Acute lung injury: Epidemiology, pathogenesis, and treatment. J Aerosol Med Pulm Drug Deliv 23: 243-252, 2010.

37. Porporato PE, Filigheddu N, Pedro JMB, Kroemer G and Galluzzi L: Mitochondrial metabolism and cancer. Cell Res 28: 265-280, 2018.
38. Bar-Ziv R, Bolas T and Dillin A: Systemic effects of mitochondrial stress. EMBO Rep 21: e50094, 2020.
39. Anderson AJ, Jackson TD, Stroud DA and Stojanovski D: Mitochondria-hubs for regulating cellular biochemistry: Emerging concepts and networks. Open Biol 9: 190126, 2019.
40. Rowlands DJ: Mitochondria dysfunction: A novel therapeutic target in pathological lung remodeling or bystander? Pharmacol Ther 166: 96-105, 2016.
41. Wu H, Wei H, Sehgal SA, Liu L and Chen Q: Mitophagy receptors sense stress signals and couple mitochondrial dynamic machinery for mitochondrial quality control. Free Radic Biol Med 100: 199-209, 2016.
42. Gottlieb RA and Stotland A: MitoTimer: A novel protein for monitoring mitochondrial turnover in the heart. J Mol Med (Berl) 93: 271-278, 2015.
43. Tilokani L, Nagashima S, Paupe V and Prudent J: Mitochondrial dynamics: Overview of molecular mechanisms. Essays Biochem 62: 341-360, 2018.
44. Collins TJ, Berridge MJ, Lipp P and Bootman MD: Mitochondria are morphologically and functionally heterogeneous within cells. EMBO J 21: 1616-1627, 2002.
45. Rongvaux A: Innate immunity and tolerance toward mitochondria. Mitochondrion 41: 14-20, 2018.
46. de-Lima-Júnior JC, Souza GF, Moura-Assis A, Gaspar RS, Gaspar JM, Rocha AL, Ferrucci DL, Lima TI, Victório SC, Bonfante ILP, *et al*: Abnormal brown adipose tissue mitochondrial structure and function in IL10 deficiency. EBioMedicine 39: 436-447, 2019.
47. Vögtle FN, Burkhart JM, Gonczarowska-Jorge H, Kücükköse C, Taskin AA, Kopczynski D, Ahrends R, Mossmann D, Sickmann A, Zahedi RP and Meisinger C: Landscape of submitochondrial protein distribution. Nat Commun 8: 290, 2017.
48. Ralto KM and Parikh SM: Mitochondria in acute kidney injury. Semin Nephrol 36: 8-16, 2016.
49. Abate M, Festa A, Falco M, Lombardi A, Luce A, Grimaldi A, Zappavigna S, Sperlongano P, Irace C, Caraglia M and Misso G: Mitochondria as playmakers of apoptosis, autophagy and senescence. Semin Cell Dev Biol 98: 139-153, 2020.
50. Cogliati S, Enriquez JA and Scorrano L: Mitochondrial cristae: Where beauty meets functionality. Trends Biochem Sci 41: 261-273, 2016.
51. Rath S, Sharma R, Gupta R, Ast T, Chan C, Durham TJ, Goodman RP, Grabarek Z, Haas ME, Hung WHW, *et al*: MitoCarta3.0: An updated mitochondrial proteome now with sub-organelle localization and pathway annotations. Nucleic Acids Res 49: D1541-D1547, 2021.
52. Smith AC and Robinson AJ: MitoMiner v3.1, an update on the mitochondrial proteomics database. Nucleic Acids Res 44 (D1): D1258-D1261, 2016.
53. Rhee HW, Zou P, Udeshi ND, Martell JD, Mootha VK, Carr SA and Ting AY: Proteomic mapping of mitochondria in living cells via spatially restricted enzymatic tagging. Science 339: 1328-1331, 2013.
54. Hartl FU and Neupert W: Protein sorting to mitochondria: Evolutionary conservations of folding and assembly. Science 247: 930-938, 1990.
55. Wiedemann N and Pfanner N: Mitochondrial machineries for protein import and assembly. Annu Rev Biochem 86: 685-714, 2017.
56. Boczonadi V, Ricci G and Horvath R: Mitochondrial DNA transcription and translation: Clinical syndromes. Essays Biochem 62: 321-340, 2018.
57. Gilkerson RW, Selker JM and Capaldi RW: The cristal membrane of mitochondria is the principal site of oxidative phosphorylation. FEBS Lett 546: 355-358, 2003.
58. Youle RJ: Mitochondria-striking a balance between host and endosymbiont. Science 365: eaaw9855, 2019.
59. Aw WC, Towarnicki SG, Melvin RG, Youngson NA, Garvin MR, Hu Y, Nielsen S, Thomas T, Pickford R, Bustamante S, *et al*: Genotype to phenotype: Diet-by-mitochondrial DNA haplotype interactions drive metabolic flexibility and organismal fitness. PLoS Genet 14: e1007735, 2018.
60. Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, Feeney C, Horvath R, Yu-Wai-Man P, Chinnery PF, *et al*: Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 77: 753-759, 2015.
61. Melvin RG and Ballard JW: Intraspecific variation in survival and mitochondrial oxidative phosphorylation in wild-caught *Drosophila* simulans. Aging Cell 5: 225-233, 2006.
62. Princepe D and De Aguiar MAM: Modeling Mito-nuclear compatibility and its role in species identification. Syst Biol 70: 133-144, 2021.
63. Telschow A, Gadau J, Werren J and Kobayashi Y: Genetic incompatibilities between mitochondria and nuclear genes: Effect on gene flow and speciation. Front Genet 10: 62, 2019.
64. Roth KG, Mambetsariev I, Kulkarni P and Salgia R: The mitochondrion as an emerging therapeutic target in cancer. Trends Mol Med 26: 119-134, 2020.
65. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES and Wang X: Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell 91: 479-489, 1997.
66. Liu X, Kim CN, Yang J, Jemmerson R and Wang X: Induction of apoptotic program in cell-free extracts: Requirement for dATP and cytochrome c. Cell 86: 147-157, 1996.
67. Bossy-Wetzel E, Newmeyer DD and Green DR: Mitochondrial cytochrome c release in apoptosis occurs upstream of DEVD-specific caspase activation and independently of mitochondrial transmembrane depolarization. EMBO J 17: 37-49, 1998.
68. Hine C, Harputlugil E, Zhang Y, Ruckenstuhl C, Lee BC, Brace L, Longchamp A, Treviño-Villarreal JH, Mejia P, Ozaki CK, *et al*: Endogenous hydrogen sulfide production is essential for dietary restriction benefits. Cell 160: 132-144, 2015.
69. Eisner V, Picard M and Hajnóczky G: Mitochondrial dynamics in adaptive and maladaptive cellular stress responses. Nat Cell Biol 20: 755-765, 2018.
70. Mitra K, Wunder C, Roysam B, Lin G and Lippincott-Schwartz J: A hyperfused mitochondrial state achieved at G1-S regulates cyclin E buildup and entry into S phase. Proc Natl Acad Sci USA 106: 11960-11965, 2009.
71. Rambold A, Kostelecky B, Elia N and Lippincott-Schwartz J: Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation. Proc Natl Acad Sci USA 108: 10190-10195, 2011.
72. Aiello A, Cristofaro M, Carrozza F, Verdone F and Carile L: Lymphocyte subpopulations and the soluble interleukin-2 receptor in Hashimoto's thyroiditis and subacute thyroiditis. Clin Ter 133: 401-404, 1990 (In Italian).
73. Leduc-Gaudet JP, Hussain SNA, Barreiro E and Gouspillou G: Mitochondrial dynamics and mitophagy in skeletal muscle health and aging. Int J Mol Sci 22: 8179, 2021.
74. Santel A, Frank S, Gaume B, Herrler M, Youle RJ and Fuller MT: Mitofusin-1 protein is a generally expressed mediator of mitochondrial fusion in mammalian cells. J Cell Sci 116: 2763-2774, 2003.
75. Eura Y, Ishihara N, Yokota S and Mihara K: Two mitofusin proteins, mammalian homologues of FZO, with distinct functions are both required for mitochondrial fusion. J Biochem 134: 333-344, 2003.
76. de Brito OM and Scorrano L: Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 456: 605-610, 2008.
77. Detmer SA and Chan DC: Complementation between mouse Mfn1 and Mfn2 protects mitochondrial fusion defects caused by CMT2A disease mutations. J Cell Biol 176: 405-414, 2007.
78. Ehses S, Raschke I, Mancuso G, Bernacchia A, Geimer S, Tondera D, Martinou JC, Westermann B, Rugarli EI and Langer T: Regulation of OPA1 processing and mitochondrial fusion by m-AAA protease isoenzymes and OMA1. J Cell Biol 187: 1023-1036, 2009.
79. Mishra P, Carelli V, Manfredi G and Chan DC: Proteolytic cleavage of Opa1 stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation. Cell Metab 19: 630-641, 2014.
80. Schlattner U, Tokarska-Schlattner M, Ramirez S, Tyurina YY, Amoscato AA, Mohammadyani D, Huang Z, Jiang J, Yanamala N, Seffouh A, *et al*: Dual function of mitochondrial Nm23-H4 protein in phosphotransfer and intermembrane lipid transfer: A cardiolipin-dependent switch. J Biol Chem 288: 111-121, 2013.
81. Griparic L, van der Wel NN, Orozco IJ, Peters PJ and van der Bliek AM: Loss of the intermembrane space protein Mgm1/OPA1 induces swelling and localized constrictions along the lengths of mitochondria. J Biol Chem 279: 18792-18798, 2004.
82. Pernas L and Scorrano L: Mito-morphosis: Mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. Annu Rev Physiol 78: 505-531, 2016.

83. Margineantu DH, Gregory Cox W, Sundell L, Sherwood SW, Beechem JM and Capaldi RA: Cell cycle dependent morphology changes and associated mitochondrial DNA redistribution in mitochondria of human cell lines. Mitochondrion 1: 425-435, 2002.
84. Mitra K: Mitochondrial fission-fusion as an emerging key regulator of cell proliferation and differentiation. Bioessays 35: 955-964, 2013.
85. Diebold L and Chandel NS: Mitochondrial ROS regulation of proliferating cells. Free Radic Biol Med 100: 86-93, 2016.
86. Jheng HF, Tsai PJ, Guo S, Kuo LH, Chang CS, Su IJ, Chang CR and Tsai YS: Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol Cell Biol 32: 309-319, 2012.
87. Deng X, Liu J, Liu L, Sun X, Huang J and Dong J: Drp1-mediated mitochondrial fission contributes to baicalein-induced apoptosis and autophagy in lung cancer via activation of AMPK signaling pathway. Int J Biol Sci 16: 1403-1416, 2020.
88. Zhang H, Yan Q, Wang X, Chen X, Chen Y, Du J and Chen L: The role of mitochondria in liver ischemia-reperfusion injury: From aspects of mitochondrial oxidative stress, mitochondrial fission, mitochondrial membrane permeable transport pore formation, mitophagy, and mitochondria-related protective measures. Oxid Med Cell Longev 2021: 6670579, 2021.
89. Smirnova E, Griparic L, Shurland DL and van der Bliek AM: Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol Biol Cell 12: 2245-2256, 2001.
90. Kraus F and Ryan MY: The constriction and scission machineries involved in mitochondrial fission. J Cell Sci 130: 2953-2960, 2017.
91. Gandre-Babbe S and van der Bliek AM: The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell 19: 2402-2412, 2008.
92. Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE and Ryan MT: MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO Rep 12: 565-573, 2011.
93. Losón OC, Song Z, Chen H and Chan DC: Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol Biol Cell 24: 659-667, 2013.
94. Chakrabarti R, Ji WK, Stan RV, de Juan Sanz J, Ryan TA and Higgs HN: INF2-mediated actin polymerization at the ER stimulates mitochondrial calcium uptake, inner membrane constriction, and division. J Cell Biol 217: 251-268, 2018.
95. Kameoka S, Adachi Y, Okamoto K, Iijima M and Sesaki H: Phosphatidic acid and cardiolipin coordinate mitochondrial dynamics. Trends Cell Biol 28: 67-76, 2018.
96. Lee H and Yoon Y: Transient contraction of mitochondria induces depolarization through the inner membrane dynamin OPA1 protein. J Biol Chem 289: 11862-11872, 2014.
97. Cho B, Cho HM, Jo Y, Kim HD, Song M, Moon C, Kim H, Kim K, Sesaki H, Rhyu IJ, *et al*: Constriction of the mitochondrial inner compartment is a priming event for mitochondrial division. Nat Commun 8: 15754, 2017.
98. Ding C, Wu Z, Huang L, Wang Y, Xue J, Chen S, Deng Z, Wang L, Song Z and Chen S: Mitofilin and CHCHD6 physically interact with Sam50 to sustain cristae structure. Sci Rep 5: 16064, 2015.
99. Niu J, Yu M, Wang C and Xu Z: Leucine-rich repeat kinase 2 disturbs mitochondrial dynamics via dynamin-like protein. J Neurochem 122: 650-658, 2012.
100. Haile Y, Deng X, Ortiz-Sandoval C, Tahbaz N, Janowicz A, Lu JQ, Kerr BJ, Gutowski NJ, Holley JE, Eggleton P, *et al*: Rab32 connects ER stress to mitochondrial defects in multiple sclerosis. J Neuroinflammation 14: 19, 2017.
101. Mohsin M, Tabassum G, Ahmad S, Ali S and Ali Syed M: The role of mitophagy in pulmonary sepsis. Mitochondrion 59: 63-75, 2021.
102. Matsuda N, Sato S, Shiba K, Okatsu K, Saisho K, Gautier CA, Sou YS, Saiki S, Kawajiri S, Sato F, *et al*: PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. J Cell Biol 189: 211-221, 2010.
103. Narendra D, Tanaka A, Suen DF and Youle RJ: Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol 183: 795-803, 2008.
104. Bingol B and Sheng M: Mechanisms of mitophagy: PINK1, Parkin, USP30 and beyond. Free Radic Biol Med 100: 210-222, 2016.
105. Sharma A, Ahmad S, Ahmad T, Ali S and Syed MA: Mitochondrial dynamics and mitophagy in lung disorders. Life Sci 284: 119876, 2021.
106. Chen Y and Dorn GW II: PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. Science 340: 471-475, 2013.
107. Glauser L, Sonnay S, Stafa K and Moore DJ: Parkin promotes the ubiquitination and degradation of the mitochondrial fusion factor mitofusin 1. J Neurochem 118: 636-645, 2011.
108. López-Doménech G, Covill-Cooke C, Ivankovic D, Halff EF, Sheehan DF, Norkett R, Birsa N and Kittler JT: Miro proteins coordinate microtubule- and actin-dependent mitochondrial transport and distribution. EMBO J 37: 321-336, 2018.
109. Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ and Springer W: PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol 12: 119-131, 2010.
110. Real P, Benito A, Cuevas J, Berciano MT, de Juan A, Coffer P, Gomez-Roman J, Lafarga M, Lopez-Vega JM and Fernandez-Luna JL: Blockade of epidermal growth factor receptors chemosensitizes breast cancer cells through up-regulation of Bnip3L. Cancer Res 65: 8151-8157, 2005.
111. Hanna RA, Quinsay MN, Orogo AM, Giang K, Rikka S and Gustafsson ÅB: Microtubule-associated protein 1 light chain 3 (LC3) interacts with Bnip3 protein to selectively remove endoplasmic reticulum and mitochondria via autophagy. J Biol Chem 287: 19094-19104, 2012.
112. Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R, Qi W, *et al*: Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14: 177-185, 2012.
113. Sekine S, Kanamaru Y, Koike M, Nishihara A, Okada M, Kinoshita H, Kamiyama M, Maruyama J, Uchiyama Y, Ishihara N, *et al*: Rhomboid protease PARL mediates the mitochondrial membrane potential loss-induced cleavage of PGAM5. J Biol Chem 287: 34635-34645, 2012.
114. Kagan VE, Jiang J, Huang Z, Tyurina YY, Desbourdes C, Cottet-Rousselle C, Dar HH, Verma M, Tyurin VA, Kapralov AA, *et al*: NDPK-D (NM23-H4)-mediated externalization of cardiolipin enables elimination of depolarized mitochondria by mitophagy. Cell Death Differ 23: 1140-1151, 2016.
115. Wei Y, Chiang WC, Sumpter R Jr, Mishra P and Levine B: Prohibitin 2 is an inner mitochondrial membrane mitophagy receptor. Cell 168: 224-238.e10, 2017.
116. Di Rita A, Peschiaroli A, D Acunzo P, Strobbe D, Hu Z, Gruber J, Nygaard M, Lambrughi M, Melino G, Papaleo E, *et al*: HUWE1 E3 ligase promotes PINK1/PARKIN-independent mitophagy by regulating AMBRA1 activation via IKKα. Nat Commun 9: 3755, 2018.
117. Ju L, Chen S, Alimujiang M, Bai N, Yan H, Fang Q, Han J, Ma X, Yang Y and Jia W: A novel role for Bcl2l13 in promoting beige adipocyte biogenesis. Biochem Biophys Res Commun 506: 485-491, 2018.
118. Murakawa T, Yamaguchi O, Hashimoto A, Hikoso S, Takeda T, Oka T, Yasui H, Ueda H, Akazawa Y, Nakayama H, *et al*: Bcl-2-like protein 13 is a mammalian Atg32 homologue that mediates mitophagy and mitochondrial fragmentation. Nat Commun 6: 7527, 2015.
119. Benard G and Rossignol R: Ultrastructure of the mitochondrion and its bearing on function and bioenergetics. Antioxid Redox Signal 10: 1313-1342, 2008.
120. Goncalves RL, Quinlan CL, Perevoshchikova IV, Hey-Mogensen M and Brand MD: Sites of superoxide and hydrogen peroxide production by muscle mitochondria assessed ex vivo under conditions mimicking rest and exercise. J Biol Chem 290: 209-227, 2015.
121. Zuo L and Wijegunawardana D: Redox role of ROS and inflammation in pulmonary diseases. Adv Exp Med Biol 1304: 187-204, 2021.
122. Moncada S and Erusalimsky JD: Does nitric oxide modulate mitochondrial energy generation and apoptosis? Nat Rev Mol Cell Biol 3: 214-220, 2002.
123. Gellerich FN, Trumbeckaite S, Opalka JR, Gellerich JF, Chen Y, Neuhof C, Redl H, Werdan K and Zierz S: Mitochondrial dysfunction in sepsis: Evidence from bacteraemic baboons and endotoxaemic rabbits. Biosci Rep 22: 99-113, 2002.

124. Adrie C, Bachelet M, Vayssier-Taussat M, Russo-Marie F, Bouchaert I, Adib-Conquy M, Cavaillon JM, Pinsky MR, Dhainaut JF and Polla BS: Mitochondrial membrane potential and apoptosis peripheral blood monocytes in severe human sepsis. Am J Respir Crit Care Med 164: 389-395, 2001.
125. Callahan LA and Supinski GS: Sepsis induces diaphragm electron transport chain dysfunction and protein depletion. Am J Respir Crit Care Med 172: 861-868, 2005.
126. Ayala JC, Grismaldo A, Aristizabal-Pachon AF, Mikhaylenko EV, Nikolenko VN, Mikhaleva LM, Somasundaram SG, Kirkland CE, Aliev G and Morales L: Mitochondrial dysfunction in intensive care unit patients. Curr Pharm Des 27: 3074, 2021.
127. Fakhruddin S, Alanazi W and Jackson KE: Diabetes-induced reactive oxygen species: Mechanism of their generation and role in renal injury. J Diabetes Res 2017: 8379327, 2017.
128. Stepien KM, Heaton R, Rankin S, Murphy A, Bentley J, Sexton D and Hargreaves IP: Evidence of oxidative stress and secondary mitochondrial dysfunction in metabolic and non-metabolic disorders. J Clin Med 6: 71, 2017.
129. Arulkumaran N, Deutschman CS, Pinsky MR, Zuckerbraun B, Schumacker PT, Gomez H, Gomez A, Murray P and Kellum JA; ADQI XIV Workgroup: Mitochondrial function in sepsis. Shock 45: 271-281, 2016.
130. Boulos M, Astiz ME, Barua RS and Osman M: Impaired mitochondrial function induced by serum from septic shock patients is attenuated by inhibition of nitric oxide synthase and poly(ADP-ribose) synthase. Crit Care Med 31: 353-358, 2003.
131. Orrenius S, Gogvadze V and Zhivotovsky B: Calcium and mitochondria in the regulation of cell death. Biochem Biophys Res Commun 460: 72-81, 2015.
132. Sharma P and Sampath H: Mitochondrial DNA integrity: Role in health and disease. Cells 8: 100, 2019.
133. Zorov DB, Juhaszova M and Sollott SJ: Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 94: 909-950, 2014.
134. Shadel GS and Horvath TL: Mitochondrial ROS signaling in organismal homeostasis. Cell 163: 560-569, 2015.
135. Poderoso JL: The formation of peroxynitrite in the applied physiology of mitochondrial nitric oxide. Arch Biochem Biophys 484: 214-220, 2009.
136. Sies H: Oxidative stress: A concept in redox biology and medicine. Redox Biol 4: 180-183, 2015.
137. Chow CW, Herrera Abreu MT, Suzuki T and Downey GP: Oxidative stress and acute lung injury. Am J Respir Cell Mol Biol 29: 427-431, 2003.
138. Puri G and Naura AS: Critical role of mitochondrial oxidative stress in acid aspiration induced ALI in mice. Toxicol Mech Methods 30: 266-274, 2020.
139. Lopez-Crisosto C, Pennanen C, Vasquez-Trincado C, Morales PE, Bravo-Sagua R, Quest AFG, Chiong M and Lavandero S: Sarcoplasmic reticulum-mitochondria communication in cardiovascular pathophysiology. Nat Rev Cardiol 14: 342-360, 2017.
140. Kwong JQ, Huo J, Bround MJ, Boyer JG, Schwanekamp JA, Ghazal N, Maxwell JT, Jang YC, Khuchua Z, Shi K, *et al*: The mitochondrial calcium uniporter underlies metabolic fuel preference in skeletal muscle. JCI Insight 3: e121689, 2018.
141. Sommakia S, Houlihan PR, Deane SS, Simcox JA, Torres NS, Jeong MY, Winge DR, Villanueva CJ and Chaudhuri D: Mitochondrial cardiomyopathies feature increased uptake and diminished efflux of mitochondrial calcium. J Mol Cell Cardiol 113: 22-32, 2017.
142. Denton RM: Regulation of mitochondrial dehydrogenases by calcium ions. Biochim Biophys Acta 1787: 1309-1316, 2009.
143. Dey S, DeMazumder D, Sidor A, Foster DB and O'Rourke B: Mitochondrial ROS drive sudden cardiac death and chronic proteome remodeling in heart failure. Circ Res 123: 356-371, 2018.
144. Halestrap AP, Woodfield KY and Connern CP: Oxidative stress, thiol reagents, and membrane potential modulate the mitochondrial permeability transition by affecting nucleotide binding to the adenine nucleotide translocase. J Biol Chem 272: 3346-3354, 1997.
145. Kiefmann M, Tank S, Keller P, Börnchen C, Rinnenthal JL, Tritt MO, Schulte-Uentrop L, Olotu C, Goetz AE and Kiefmann R: IDH3 mediates apoptosis of alveolar epithelial cells type 2 due to mitochondrial Ca^{2+} uptake during hypocapnia. Cell Death Dis 8: e3005, 2017.
146. Mu G, Deng Y, Lu Z, Li X and Chen Y: miR-20b suppresses mitochondrial dysfunction-mediated apoptosis to alleviate hyperoxia-induced acute lung injury by directly targeting MFN1 and MFN2. Acta Biochim Biophys Sin (Shanghai) 53: 220-228, 2021.
147. Szturmowicz M and Demkow U: Neutrophil extracellular traps (NETs) in severe SARS-CoV-2 lung disease. Int J Mol Sci 22: 8854, 2021.
148. Lugg ST, Scott A, Parekh D, Naidu B and Thickett DR: Cigarette smoke exposure and alveolar macrophages: Mechanisms for lung disease. Thorax 77: 94-101, 2022.
149. West AP, Brodsky IE, Rahner C, Woo DK, Erdjument-Bromage H, Tempst P, Walsh MC, Choi Y, Shadel GS and Ghosh S: TLR signalling augments macrophage bactericidal activity through mitochondrial ROS. Nature 472: 476-480, 2011.
150. Yuan Z, Syed MA, Panchal D, Joo M, Colonna M, Brantly M and Sadikot RT: Triggering receptor expressed on myeloid cells 1 (TREM-1)-mediated Bcl-2 induction prolongs macrophage survival. J Biol Chem 289: 15118-15129, 2014.
151. Guillén-Gómez E, Silva I, Serra N, Caballero F, Leal J, Breda A, San Martín R, Pastor-Anglada M, Ballarín JA, Guirado L and Díaz-Encarnación MM: From inflammation to the onset of fibrosis through A_{2A} receptors in kidneys from deceased donors. Int J Mol Sci 21: 8826, 2020.
152. Pearce EL, Poffenberger MC, Chang CH and Jones RG: Fueling immunity: Insights into metabolism and lymphocyte function. Science 342: 1242454, 2013.
153. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Siegal GP and Abraham E: Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. Am J Respir Crit Care Med 178: 168-179, 2008.
154. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, Rowlands DJ, Quadri SK, Bhattacharya S and Bhattacharya J: Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. Nat Med 18: 759-765, 2012.
155. Yu J, Shi J, Wang D, Dong S, Zhang Y, Wang M, Gong L, Fu Q and Liu D: Heme oxygenase-1/carbon monoxide-regulated mitochondrial dynamic equilibrium contributes to the attenuation of endotoxin-induced acute lung injury in rats and in lipopolysaccharide-activated macrophages. Anesthesiology 125: 1190-1201, 2016.
156. Shi J, Yu J, Zhang Y, Wu L, Dong S, Wu L, Wu L, Du S, Zhang Y and Ma D: PI3K/Akt pathway-mediated HO-1 induction regulates mitochondrial quality control and attenuates endotoxin-induced acute lung injury. Lab Invest 99: 1795-1809, 2019.
157. Yu J, Wang Y, Li Z, Dong S, Wang D, Gong L, Shi J, Zhang Y, Liu D and Mu R: Effect of heme oxygenase-1 on mitofusin-1 protein in LPS-induced ALI/ARDS in rats. Sci Rep 6: 36530, 2016.
158. Deng S, Zhang L, Mo Y, Huang Y, Li W, Peng Q, Huang L and Ai Y: Mdivi-1 attenuates lipopolysaccharide-induced acute lung injury by inhibiting MAPKs, oxidative stress and apoptosis. Pulm Pharmacol Ther 62: 101918, 2020.
159. Jiang C, Zhang J, Xie H, Guan H, Li R, Chen C, Dong H, Zhou Y and Zhang W: Baicalein suppresses lipopolysaccharide-induced acute lung injury by regulating Drp1-dependent mitochondrial fission of macrophages. Biomed Pharmacother 145: 112408, 2022.
160. Shi J, Yu T, Song K, Du S, He S, Hu X, Li X, Li H, Dong S, Zhang Y, *et al*: Dexmedetomidine ameliorates endotoxin-induced acute lung injury in vivo and in vitro by preserving mitochondrial dynamic equilibrium through the HIF-1a/HO-1 signaling pathway. Redox Biol 41: 101954, 2021.
161. Wu D, Zhang H, Wu Q, Li F, Wang Y, Liu S and Wang J: Sestrin 2 protects against LPS-induced acute lung injury by inducing mitophagy in alveolar macrophages. Life Sci 267: 118941, 2021.
162. Liu W, Li CC, Lu X, Bo LY and Jin FG: Overexpression of transcription factor EB regulates mitochondrial autophagy to protect lipopolysaccharide-induced acute lung injury. Chin Med J (Engl) 132: 1298-1304, 2019.
163. Luo X, Liu R, Zhang Z, Chen Z, He J and Liu Y: Mitochondrial division inhibitor 1 attenuates mitophagy in a rat model of acute lung injury. Biomed Res Int 2019: 2193706, 2019.
164. Liu W, Li Y, Bo L, Li C and Jin F: Positive regulation of TFEB and mitophagy by PGC-1α to alleviate LPS-induced acute lung injury in rats. Biochem Biophys Res Commun 577: 1-5, 2021.

165. Zhao R, Wang B, Wang D, Wu B, Ji P and Tan D: Oxyberberine prevented lipopolysaccharide-induced acute lung injury through inhibition of mitophagy. Oxid Med Cell Longev 2021: 6675264, 2021.
166. Zhang Z, Chen Z, Liu R, Liang Q, Peng Z, Yin S, Tang J, Gong T and Liu Y: Bcl-2 proteins regulate mitophagy in lipopolysaccharide-induced acute lung injury via PINK1/Parkin signaling pathway. Oxid Med Cell Longev 2020: 6579696, 2020.
167. Patel S: Danger-associated molecular patterns (DAMPs): The derivatives and triggers of inflammation. Curr Allergy Asthma Rep 18: 63, 2018.
168. Frevert C, Felgenhauer J, Wygrecka M, Nastase M and Schaefer L: Danger-associated molecular patterns derived from the extracellular matrix provide temporal control of innate immunity. J Histochem Cytochem 66: 213-227, 2018.
169. Vénéreau E, Ceriotti C and Bianchi ME: DAMPs from cell death to new life. Front Immunol 6: 422, 2015.
170. Bianchi ME: DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 81: 1-5, 2007.
171. Zedler S and Faist E: The impact of endogenous triggers on trauma-associated inflammation. Curr Opin Crit Care 12: 595-601, 2006.
172. Vourc'h M, Roquilly A and Asehnoune K: Trauma-induced damage-associated molecular patterns-mediated remote organ injury and immunosuppression in the acutely Ill patient. Front Immunol 9: 1330, 2018.
173. West AP and Shadel GS: Mitochondrial DNA in innate immune responses and inflammatory pathology. Nat Rev Immunol 17: 363-375, 2017.
174. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K and Hauser CJ: Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 464: 104-107, 2010.
175. Lu B, Kwan K, Levine YA, Olofsson PS, Yang H, Li J, Joshi S, Wang H, Andersson U, Chavan SS and Tracey KJ: α7 Nicotinic acetylcholine receptor signaling inhibits inflammasome activation by preventing mitochondrial DNA release. Mol Med 20: 350-358, 2014.
176. Oka T, Hikoso S, Yamaguchi O, Taneike M, Takeda T, Tamai T, Oyabu J, Murakawa T, Nakayama H, Nishida K, *et al*: Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. Nature 485: 251-255, 2012.
177. Zhang L, Deng S, Zhao S, Ai Y, Zhang L, Pan P, Su X, Tan H and Wu D: Intra-peritoneal administration of mitochondrial DNA provokes acute lung injury and systemic inflammation via Toll-like receptor 9. Int J Mol Sci 17: 1425, 2016.
178. Sun S, Sursal T, Adibnia Y, Zhao C, Zheng Y, Li H, Otterbein LE, Hauser CJ and Itagaki K: Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. PLoS One 8: e59989, 2013.
179. Gonzalez AS, Elguero ME, Finocchietto P, Holod S, Romorini L, Miriuka SG, Peralta JG, Poderoso JJ and Carreras MC: Abnormal mitochondrial fusion-fission balance contributes to the progression of experimental sepsis. Free Radic Res 48: 769-783, 2014.
180. Chen H, Lin H, Dong B, Wang Y, Yu Y and Xie K: Hydrogen alleviates cell damage and acute lung injury in sepsis via PINK1/Parkin-mediated mitophagy. Inflamm Res 70: 915-930, 2021.
181. Chang AL, Ulrich A, Suliman HB and Piantadosi CA: Redox regulation of mitophagy in the lung during murine staphylococcus aureus sepsis. Free Radic Biol Med 78: 179-189, 2015.
182. Mannam P, Shinn AS, Srivastava A, Neamu RF, Walker WE, Bohanon M, Merkel J, Kang MJ, Dela Cruz CS, Ahasic AM, *et al*: MKK3 regulates mitochondrial biogenesis and mitophagy in sepsis-induced lung injury. Am J Physiol Lung Cell Mol Physiol 306: L604-L619, 2014.
183. Westphalen K, Monma E, Islam MN and Bhattacharya J: Acid contact in the rodent pulmonary alveolus causes proinflammatory signaling by membrane pore formation. Am J Physiol Lung Cell Mol Physiol 303: L107-L116, 2012.
184. Kuebler WM, Parthasarathi K, Wang PM and Bhattacharya J: A novel signaling mechanism between gas and blood compartments of the lung. J Clin Invest 105: 905-913, 2000.
185. Hough RF, Islam MN, Gusarova GA, Jin G, Das S and Bhattacharya J: Endothelial mitochondria determine rapid barrier failure in chemical lung injury. JCI Insight 4: e124329, 2019.
186. Ogino K, Nagaoka K, Okuda T, Oka A, Kubo M, Eguchi E and Fujikura Y: PM2.5-induced airway inflammation and hyperresponsiveness in NC/Nga mice. Environ Toxicol 32: 1047-1054, 2017.
187. Wei T and Tang M: Biological effects of airborne fine particulate matter ($PM_{2.5}$) exposure on pulmonary immune system. Environ Toxicol Pharmacol 60: 195-201, 2018.
188. Xu M, Li F, Wang M, Zhang H, Xu L, Adcock IM, Chung KF and Zhang Y: Protective effects of VGX-1027 in $PM_{2.5}$-induced airway inflammation and bronchial hyperresponsiveness. Eur J Pharmacol 842: 373-383, 2019.
189. Kalogeris T, Baines CP, Krenz M and Korthuis RJ: Ischemia/reperfusion. Compr Physiol 7: 113-170, 2016.
190. Tai H, Jiang X, Song N, Xiao HH, Li Y, Cheng MJ, Yin XM, Chen YR, Yang GL, Jiang XY, *et al*: Tanshinone IIA combined with cyclosporine a alleviates lung apoptosis induced by renal ischemia-reperfusion in obese rats. Front Med (Lausanne) 8: 617393, 2021.
191. Zhang Y, Yu G, Kaminski N and Lee PJ: PINK1 mediates the protective effects of thyroid hormone T3 in hyperoxia-induced lung injury. Am J Physiol Lung Cell Mol Physiol 320: L1118-L1125, 2021.
192. Supinski GS, Schroder EA and Callahan LA: Mitochondria and critical illness. Chest 157: 310-322, 2020.
193. Powers SK, Hudson MB, Nelson WB, Talbert EE, Min K, Szeto HH, Kavazis AN and Smuder AJ: Mitochondria-targeted antioxidants protect against mechanical ventilation-induced diaphragm weakness. Crit Care Med 39: 1749-1759, 2011.
194. Miglio G, Rosa AC, Rattazzi L, Collino M, Lombardi G and Fantozzi R: PPARgamma stimulation promotes mitochondrial biogenesis and prevents glucose deprivation-induced neuronal cell loss. Neurochem Int 55: 496-504, 2009.
195. Moskowitzova K, Orfany A, Liu K, Ramirez-Barbieri G, Thedsanamoorthy JK, Yao R, Guariento A, Doulamis IP, Blitzer D, Shin B, *et al*: Mitochondrial transplantation enhances murine lung viability and recovery after ischemia-reperfusion injury. Am J Physiol Lung Cell Mol Physiol 318: L78-L88, 2020.
196. Ramachandran A and Jaeschke H: Acetaminophen toxicity: Novel insights into mechanisms and future perspectives. Gene Expr 18: 19-30, 2018.
197. Tan DX, Manchester LC, Qin L and Reiter RJ: Melatonin: A mitochondrial targeting molecule involving mitochondrial protection and dynamics. Int J Mol Sci 17: 2124, 2016.
198. Srinivasan V, Pandi-Perumal SR, Spence DW, Kato H and Cardinali DP: Melatonin in septic shock: Some recent concepts. J Crit Care 25: 656.e1-e6, 2010.
199. Vance JE: Phospholipid synthesis and transport in mammalian cells. Traffic 16: 1-18, 2015.
200. Adachi Y, Itoh K, Yamada T, Cerveny KL, Suzuki TL, Macdonald P, Frohman MA, Ramachandran R, Iijima M and Sesaki H: Coincident phosphatidic acid interaction restrains Drp1 in mitochondrial division. Mol Cell 63: 1034-1043, 2016.
201. Macdonald PJ, Francy CA, Stepanyants N, Lehman L, Baglio A, Mears JA, Qi X and Ramachandran R: Distinct splice variants of dynamin-related protein 1 differentially utilize mitochondrial fission factor as an effector of cooperative GTPase activity. J Biol Chem 291: 493-507, 2016.
202. Ban T, Heymann JA, Song Z, Hinshaw JE and Chan DC: OPA1 disease alleles causing dominant optic atrophy have defects in cardiolipin-stimulated GTP hydrolysis and membrane tubulation. Hum Mol Genet 19: 2113-2122, 2010.
203. Ugarte-Uribe B, Müller HM, Otsuki M, Nickel W and García-Sáez AJ: Dynamin-related protein 1 (Drp1) promotes structural intermediates of membrane division. J Biol Chem 289: 30645-30656, 2014.
204. Bustillo-Zabalbeitia I, Montessuit S, Raemy E, Basañez G, Terrones O and Martinou J: Specific interaction with cardiolipin triggers functional activation of dynamin-related protein 1. PLoS One 9: e102738, 2014.
205. Adachi Y, Iijima M and Sesaki H: An unstructured loop that is critical for interactions of the stalk domain of Drp1 with saturated phosphatidic acid. Small GTPases 9: 472-479, 2018.
206. Qi X, Disatnik MH, Shen N, Sobel RA and Mochly-Rosen D: Aberrant mitochondrial fission in neurons induced by protein kinase C{delta} under oxidative stress conditions in vivo. Mol Biol Cell 22: 256-265, 2011.
207. Kim DI, Lee KH, Gabr AA, Choi GE, Kim JS, Ko SH and Han HJ: Aβ-Induced Drp1 phosphorylation through Akt activation promotes excessive mitochondrial fission leading to neuronal apoptosis. Biochim Biophys Acta 1863: 2820-2834, 2016.

208. Xu S, Wang P, Zhang H, Gong G, Gutierrez Cortes N, Zhu W, Yoon Y, Tian R and Wang W: CaMKII induces permeability transition through Drp1 phosphorylation during chronic β-AR stimulation. Nat Commun 7: 13189, 2016.
209. Niemann A, Ruegg M, La Padula V, Schenone A and Suter U: Ganglioside-induced differentiation associated protein 1 is a regulator of the mitochondrial network: New implications for charcot-marie-tooth disease. J Cell Biol 170: 1067-1078, 2005.
210. Tondera D, Santel A, Schwarzer R, Dames S, Giese K, Klippel A and Kaufmann J: Knockdown of MTP18, a novel phosphatidylinositol 3-kinase-dependent protein, affects mitochondrial morphology and induces apoptosis. J Biol Chem 279: 31544-31555, 2004.
211. Norton M, Ng AC, Baird S, Dumoulin A, Shutt T, Mah N, Andrade-Navarro MA, McBride HM and Screaton RA: ROMO1 is an essential redox-dependent regulator of mitochondrial dynamics. Sci Signal 7: ra10, 2014.
212. Zoulikha M, Xiao Q, Boafo GF, Sallam MA, Chen Z and He W: Pulmonary delivery of siRNA against acute lung injury/acute respiratory distress syndrome. Acta Pharm Sin B 12: 600-620, 2022.
213. Singer M: The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. Virulence 5: 66-72, 2014.
214. Hsu YC, Wu YT, Yu TH and Wei YH: Mitochondria in mesenchymal stem cell biology and cell therapy: From cellular differentiation to mitochondrial transfer. Semin Cell Dev Biol 52: 119-131, 2016.
215. Zhang H, Feng YW and Yao YM: Potential therapy strategy: Targeting mitochondrial dysfunction in sepsis. Mil Med Res 5: 41, 2018.
216. Morrison TJ, Jackson MV, Cunningham EK, Kissenpfennig A, McAuley DF, O'Kane CM and Krasnodembskaya AD: Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. Am J Respir Crit Care Med 196: 1275-1286, 2017.
217. Willson JA, Arienti S, Sadiku P, Reyes L, Coelho P, Morrison T, Rinaldi G, Dockrell DH, Whyte MKB and Walmsley SR: Neutrophil HIF-1α stabilization is augmented by mitochondrial ROS produced via the glycerol 3-phosphate shuttle. Blood 139: 281-286, 2022.