Respiratory Research

REVIEW

Open Access

# Research progress of mitochondrial dysfunction induced pyroptosis in acute lung injury

Luhan Yang[1†], Qingyi Ren[1†], Yaohui Wang[1†], Yucheng Zheng[1], Fei Du[1], Fang Wang[2], Jie Zhou[1], Linxi Gui[1], Shengdong Chen[1], Xiurui Chen[1], Wanting Zhang[1], Yuhong Sun[1], Xiaolin Zhong[2], Hao Liu[1*], Xian Jiang[3*] and Zhuo Zhang[1*]

**Abstract**

Acute lung injury (ALI) is a common critical respiratory disease in clinical practice, especially in the ICU, with a high mortality rate. The pathogenesis of ALI is relatively complex, mainly involving inflammatory response imbalance, oxidative stress, cell apoptosis, and other aspects. However, currently, the treatment measures taken based on the above mechanisms have not had significant effects. Recent research shows that mitochondrial dysfunction and pyroptosis play an important role in ALI, but there is not much analysis on the relationship between mitochondrial dysfunction and pyroptosis at present. This article reviews the situation of mitochondrial dysfunction in ALI, pyroptosis in ALI, whether mitochondrial dysfunction is related to pyroptosis in ALI, and how to do so, and further analyzes the relationship between them in ALI. This review describes how to alleviate mitochondrial dysfunction, and then suppress the associated immunological pyroptosis, providing new ideas for the clinical treatment of ALI.

**Keywords** Mitochondrial dysfunction, Pyroptosis, Acute lung injury

## Introduction

Acute lung injury (ALI) is a serious clinical syndrome characterized by diffuse alveolar cell injury, destruction of endothelial and alveolar epithelial barrier, increase of microvascular permeability, and influence of gas exchange function [1, 2]. In the ICU, the morbidity and mortality rate is as high as 40–60% [3, 4]. Both direct and indirect factors lead to ALI, such as aspiration pneumonia, pulmonary embolism, oxygen toxicity, drowning, etc., which are direct factors. Sepsis, shock, severe pancreatitis, disseminated intravascular coagulation, etc. are indirect factors [5–8].

Although symptomatic and supportive treatment can be provided for ALI, there is still a lack of effective means. Lung-protective mechanical ventilation can significantly reduce the mortality rate of this disease, but it is prone to

†Luhan Yang, Qingyi Ren and Yaohui Wang contributed equally to this work.

*Correspondence:
Hao Liu
h_lewis@126.com
Xian Jiang
354699170@qq.com
Zhuo Zhang
zhuozhang@swmu.edu.cn
[1]School of Pharmacy, Southwest Medical University, Luzhou 646000, China
[2]Department of Gastroenterology, Affiliated Hospital of Southwest Medical University, Luzhou 646000, China
[3]Department of Anesthesiology, Luzhou People's Hospital, Luzhou 646000, China

ventilator-induced lung injury [9, 10]. Medications such as diuretics, antiplatelet drugs, antioxidants, vasodilators, and glucocorticoids can improve the pathological damage of ALI, but have no significant impact on the mortality rate of ALI [11, 12]. Mesenchymal stem cells may be effective, but they are still in the experimental stage and the mechanism of action is not very clear, also stem cell-based therapy exists some worrying issues, for instance, low stability, the risk of pulmonary embolism, and tumor formation [13, 14].

The pathogenesis of ALI is complex and not fully understood, so exploring the mechanism of ALI and seeking new treatment methods based on the mechanism to improve patient prognosis and reduce mortality is very important. Oxidative stress, as one of the mechanisms of ALI, it balances the production and removal of oxygen free radicals in the lungs. Once the imbalance occurs, it will damage lung histiocyte and activate inflammatory reaction. Studies have found that mitochondrial dysfunction will increase the production of reactive oxygen free radicals. Imbalance of inflammatory response is an important cause of ALI, and when pro-inflammatory and anti-inflammatory factors are imbalanced, it will increase inflammatory cascade activation response. Mitochondrial dysfunction can induce the secretion of a large number of pro-inflammatory factors. In addition, another important mechanism of action is cell apoptosis. When proapoptotic factors dominate, a large number of cells undergo apoptosis, leading to cascading amplification effects and ultimately causing lung tissue damage. Furthermore, severe damage to cell oxygen consumption, known as cytopathic hypoxia, is one of the pathological markers of the lungs in patients with pathogen induced ALI, but its mechanism is still unclear. Mitochondrial dysfunction is involved in impaired cellular oxygen consumption, and may play an important role in the pathogenesis of ALI. Mitochondria function involves oxidative phosphorylation, tricarboxylic acid cycle, electron transport chain, maintenance of dynamic balance of $Ca^{2+}$ concentration, regulation of cell metabolism, cholesterol synthesis and some hemes [15–17]. Mitochondrial dysfunction can activate different types of cysteine aspartate specific enzymes (caspases), inducing pyroptosis of immune cells such as macrophages through classical or non-classical pyroptosis pathways, causing pores on the cell membrane, leading to cell swelling and rupture, thereby releasing interleukin(IL-)18 and interleukin(IL-)1β inflammatory factors can cause alveolar inflammation or vascular interstitial edema, participate in the occurrence and development of ALI, or promote pulmonary inflammation, leading to worsening of the patient's condition.

This article reviews mitochondrial dysfunction, pyroptosis and the relationship between them in acute lung injury, so as to provide a theoretical basis for exploring the pathogenesis of ALI and looking for potential therapeutic targets.

## Mitochondrial dysfunction and acute lung injury

As the "energy factory" of cells, mitochondria provide energy for cell life activities through a series of reactions. Moreover, mitochondria are also involved in intracellular signal transmission, biosynthesis, cell metabolism and other activities [18, 19]. Recent evidence suggests that mitochondrial dysfunction will influence the occurrence and development of ALI. Mitochondrial functions related to this disease mainly include the oxidative phosphorylation, $Ca^{2+}$ steady state, electron transfer chain, tricarboxylic acid cycle.

### Oxidative phosphorylation and ALI

Oxidative phosphorylation (OXPHOS) consists of four complexes, two mobile electron carriers, ubiquinone and cytochrome c(Cytc) [20]. It participates in ALI by inhibiting complex enzyme activity.

After lipopolysaccharide(LPS) treatment of macrophages, the activities of complex I, complex II, complex III and complex IV are inhibited, thus inhibiting the function of OXPHOS, weakening M2 activation of macrophages, and then inducing macrophages to polarize toward M1, inducing a series of inflammatory reactions, and aggravating the severity of ALI [21].

The OXPHOS function is inhibited. In addition to the reduction of ATP production, it also produces mitochondrial reactive oxygen species(ROS) through complex I, thus secreting IL-1β, Tumor necrosis factor(TNF-α) inflammatory cytokines can enhance pulmonary inflammation and exacerbate ALI [22] (Fig. 1A).

### Ca2+ homeostasis and ALI

Mitochondria are calcium storage organelle with double membranes, and $Ca^{2+}$ is distributed in their intermembrane space and matrix [23]. $Ca^{2+}$ is the second messenger of cells, closely related to cell proliferation, programmed cell death, gene transcription, signal transduction, etc [24].

$Ca^{2+}$ is involved in the regulation of ATP generation and ROS signaling, which is a key factor in regulating mitochondrial function by stimulating the Tricarboxylic acid cycle (TCA). This causes the TCA to produce nicotinamide adenine dinucleotide(NAD), which is used for the Electron transfer chain(ETC) pathway to produce ATP and nicotinamide adenine dinucleotide phosphate(NADP), which is used to eliminate ROS [25].

Through research, it has been found that $Ca^{2+}$ homeostasis imbalance participates in ALI by activating inflammatory signaling pathways, stimulating the release of

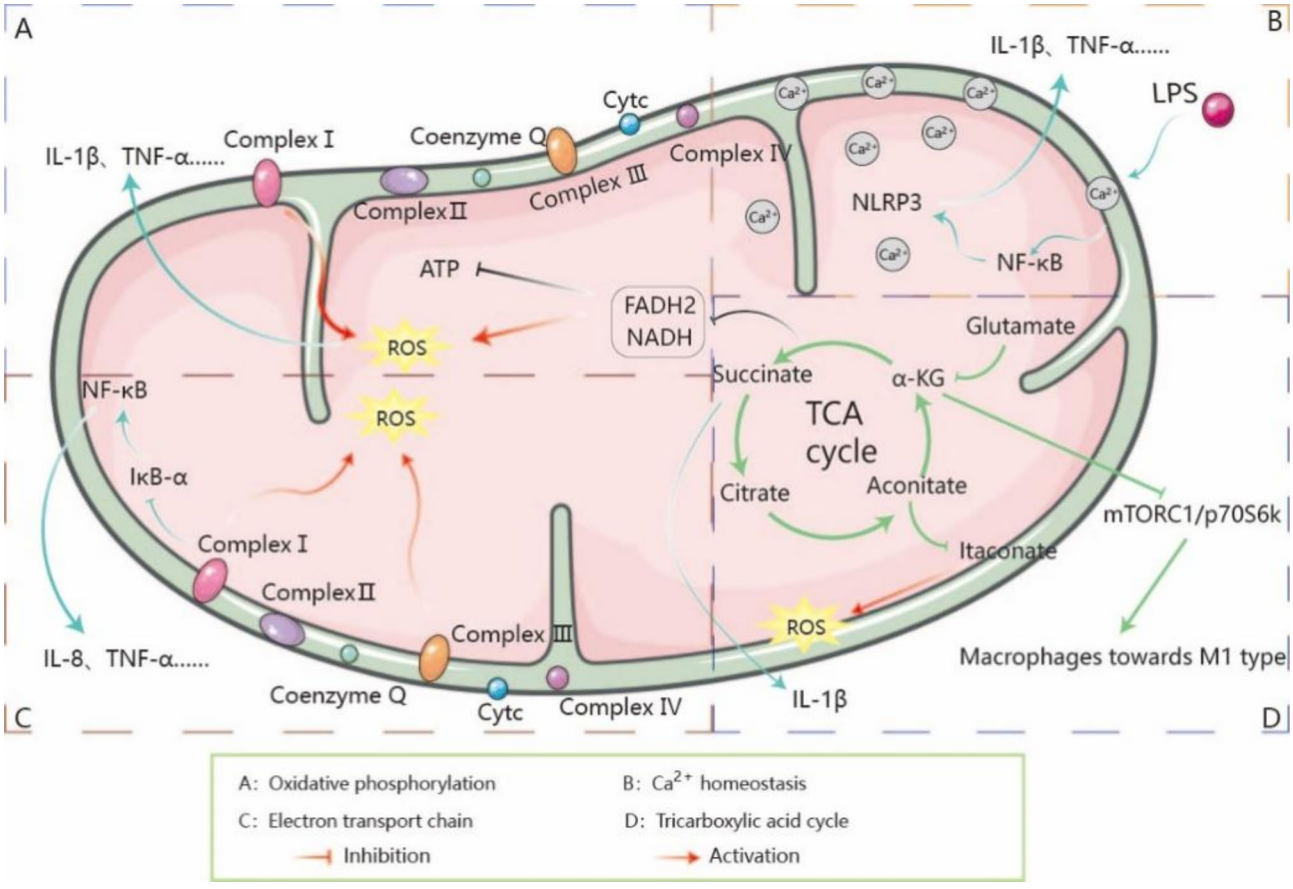


**Fig. 1** Mechanism of mitochondrial dysfunction related to acute lung injury. **A**: Oxidative phosphorylation dysfunction participates in the mechanism of ALI: Through the enhancement of complex I activity, mitochondrial ROS is produced and IL-1β is secreted, and then enhance pulmonary inflammation. **B**: The mechanism of $Ca^{2+}$ homeostasis imbalance participating in ALI: LPS induces $Ca^{2+}$ overload and regulates NF-κB activity, activates NLRP3 inflammasome, promotes the secretion of inflammatory cytokines IL-1β, TNF-α and etc. **C**: The mechanism by which electron transfer chain disorders participate in ALI: The enhanced activity of respiratory chain complex I promotes IκB- α to be degradated, thereby activating more NF-κB. Upregulate the expression of cytokines IL-8 and TNF-α can exacerbate pulmonary inflammation. In addition, it also leads to increased ROS production, exacerbating mitochondrial damage and inducing mitochondrial oxidative stress. **D**: The mechanism of involvement of tricarboxylic acid cycle disorders in ALI: Inhibition of itaconic acid production increases the generation of ROS, furthermore, the accumulation of succinic acid increases the expression of IL-1β

inflammatory mediators, and regulating the integrity of pulmonary microvascular endothelial barrier.

LPS-induced ALI can lead to an increase in macrophage cytoplasmic calcium ions, increase the activity of myeloperoxidase(MPO) in lung tissue, and regulate the activity of NF-κB and activate NLRP3 inflammasomes, promoting the secretion of the inflammatory factorTNF-α and IL-1β, can induce inflammatory reactions and exacerbate the degree of lung injury [26, 27] (Fig. 1B).

The increase in intracellular $Ca^{2+}$ concentration increases the permeability of endothelial cells, triggering a cascade reaction of vascular activation, such as increasing the expression of vascular adhesion molecules, which can lead to the release of inflammatory mediator IL-8 and exacerbate inflammation [28, 29].

## Electron transfer chain and ALI

ETC, also known as suction chain, is composed of hydrogen and electron transmitters on the inner mitochondrial membrane of eukaryotes [30]. Research has shown that respiratory chain dysfunction can participate in ALI by inducing oxidative stress, activating inflammation related protein complexes, and promoting the release of pro-inflammatory cytokines.

ETC, as the main source of cellular energy, plays an important role in the production of ATP and ROS [31]. All mitochondrial enzyme complexes can produce ROS, with the main sources of production being complex I and complex III [32]. When ETC dysfunction occurs, it will lead to increased ROS production, which will aggravate the degree of mitochondrial damage and induce mitochondrial oxidative stress. ROS mediated inflammatory reaction will cause the destruction of cytoskeleton proteins and connexins, increase the gap between

endothelial cells, cause vascular permeability, and affect the occurrence and development of ALI [33–35] (Fig. 1C).

Coenzyme Q is an important component of ETC and an important cofactor for this function, serving as an antioxidant and free radical scavenger. The lack of coenzyme Q can lead to oxidative stress and the inhibitory effect of NF-κB expression level is weakened and participates in the process of ALI [36, 37].

After LPS treatment, the activity of respiratory chain complex I increases, which will promote the degradation of IκB-α, activation of more NF-κB. Thereby regulating NF-κB dependent cytokine expression, such as IL-8 and TNF-α, aggravating pulmonary inflammation [38, 39] (Fig. 1C).

#### Tricarboxylic acid cycle and ALI

The reaction site of the TCA is in the linear granular matrix, which is an important metabolic pathway to produce cell energy and fatty acid and other biosynthetic precursors. It also provides Nicotinamide adenine dinucleotide(NADH) and Flavine adenine dinucleotide(FADH)2 for OXPHOS. When TCA is dysfunctional, it will reduce ATP and increase ROS production [40, 41].

In the early stages of ALI, inflammation can be regulated through mitochondrial TCA. Studies have shown that after stimulation with LPS, the transient accumulation of succinic acid, an intermediate product of TCA in mitochondria in macrophages during the early stages of inflammation, can lead to the increased expression of pro-inflammatory factor IL-1β and inhibition of itaconic acid production will increase the generation of ROS, ultimately inhibiting inflammatory response [42] (Fig. 1D)

After abnormal metabolism of TCA, it can participate in ALI by activating inflammation related signaling pathways, inhibiting anti-inflammatory related signaling pathways, and inhibiting fatty acid oxidation.

When glutamine metabolism is abnormal, its products α-Ketoglutaric acid(α- KG) is also decreased, inhibiting the mTORC1/p70S6K signaling pathway and weakening the inhibition of macrophage polarization towards M1 type, exacerbating pulmonary inflammation, and thus promoting the occurrence and development of ALI [43].

## Pyroptosis and acute lung injury

ALI is a clinical syndrome characterized by damage to pulmonary capillary endothelial cells and epithelial cells, with sustained damage to airway epithelium and chronic inflammation as the main markers of its pathogenesis [44]. Previous research has established that the pyroptosis of alveolar macrophages, neutrophils and natural killer cell play an significant role in the occurrence and development of ALI [45, 46].

#### Macrophage pyroptosis and ALI

Pulmonary alveolar macrophages (AM) are located on the inner surface of the lung, accounting for 55% of lung immune cells. They play an important role in natural immunity and host defense, and their phenotypic differentiation affects the process of pulmonary inflammation [47]. After being stimulated by infection and non-infection, it affects the development of ALI by synthesizing and releasing various inflammatory cytokines [48, 49].

LPS activates NLRP3 inflammasomes in macrophages. As a protein complex, inflammasomes can activate caspase-1 and promote the release of inflammatory factor IL-1β and IL-18, triggering inflammatory cascade effect, and it can damage alveolar capillary barrier, increase vascular permeability, and induce ALI [50, 51] (Fig. 2).

In addition, NLRP3-mediated macrophage pyroptosis induces the secretion of high mobility group protein B1 (HMGB1), and the increase of HMGB1 expression will positively enhance the activation of NLRP3 and further activate caspase-1, thus enhancing macrophage pyroptosis, aggravating inflammatory response, and ultimately aggravating ALI [52, 53] (Fig. 2).

In addition, experiments have shown that macrophages rely on caspase-1 to secrete pyroptosis PyrBDs, which can trigger vascular interstitial edema and enhance the inflammatory response of ALI, exacerbating lung injury [54]. (Fig. 2) The pyroptosis of macrophages also promotes the migration of neutrophils to the lungs, promoting the secretion of IL-6, IL-1β and TNF-α, exacerbating the histological manifestations of lung injury [53]. Therefore, inhibiting the inflammatory response in macrophages plays an important role in reducing the severity of ALI.

#### Neutrophil pyroptosis and ALI

Neutrophils (NE), also known as polymorphonuclear leukocytes, account for 40 -70% of the total number of white blood cells, and their cellular components mainly include antimicrobial peptides and neutrophil specific proteolytic enzymes. It has been found that neutrophil pyroptosis participates in ALI by activating inflammatory signaling pathway and releasing inflammatory cytokines.

It can produce ROS and Neutrophil Extracellular Traps (NET), so this cell has strong antibacterial and antifungal abilities and is the first immune cell to reach the site of infection or inflammation [55, 56]. Among them, NET has been identified as a potential mediator of systemic inflammatory diseases, which can exacerbate alveolar capillary barrier damage and promote the release of inflammatory cytokines. Experimental measurements have been conducted to determine the expression levels of MPO-DNA complex, caspase-1, and inflammatory cytokines in the supernatant of bronchial aspirates from ALI patients, and has been found significant differences

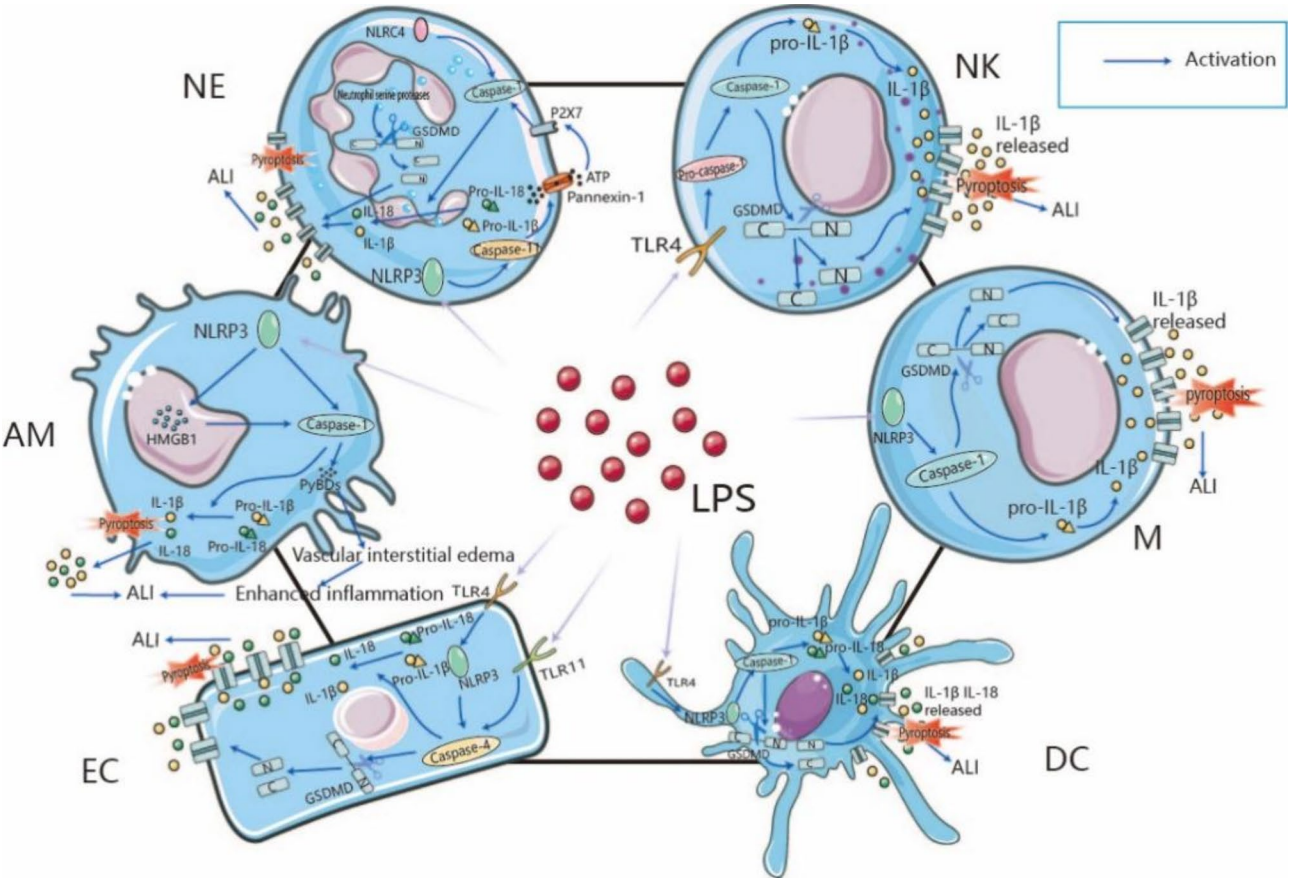


**Fig. 2** Mechanism of pyroptosis associated with acute lung injury. Neutrophils (NE): LPS activates the NLRP3/caspase-11/pannexin-1/P2×7/caspase-1 pathway, induces pyroptosis, and releases IL-1β, IL-18, leads to the occurrence and development of ALI. IL-1β and IL-18 can also be significantly increased through the NLRC-4-caspase-1 pathway, further enhancing the inflammatory response and increasing the degree of ALI damage. Macrophages (AM): LPS activates the NLRP3/caspase-1 pathway and releases IL-1β and IL-18, trigger inflammatory waterfall effect, increase vascular permeability, and induce ALI. NLRP3 also induces the secretion of high mobility group protein 1(HMBG1), activates caspase-1, enhances pyroptosis, and aggravates inflammatory reaction. Caspase-1 can secrete PyrBDs, which can trigger vascular interstitial edema and enhance ALI inflammatory response. Endothelial cells (EC): LPS induces pyroptosis and participates in ALI through TLR4/NLRP3/caspase-4 or TLR11/caspase-4. Natural killer cell (NK): LPS activates TLR4 /caspase-1 pathway, cleaves GSDMD, causes pyroptosis, and secretes IL-1β, IL-18, inducing inflammatory response. Monocytes (M): After LPS stimulation, the NLRP3/caspase-1 pathway is activated, cleaving GSDMD. Its N-terminal binds to phospholipids in the plasma membrane to form membrane pores and secrete IL-1β, enhance pulmonary inflammation and exacerbate ALI. Dendritic cells (DCs): LPS activates the TLR4 /NLRP3 /caspase-1 pathway, thereby cleaving GSDMD. Its active N-terminal oligomers and forms pores in the plasma membrane, leading to pyroptosis and secretion of IL-1β, IL-18, enhances inflammatory response and exacerbates ALI

were observed between survivors and non survivors with IL-18 and IL-1β, and MPO-DNA complexes were found there is a significant correlation to interact with caspase-1 and IL-1β. The above all indicate that NET plays an inflammatory role in ALI [57, 58].

Neutrophil serine proteases (NSPs) can activate and cleave Gasdermin D(GSDMD) independently of caspase. Functional N-terminal fragments form transmembrane pores on the plasma membrane, release inflammatory factors such as IL-18, induce inflammatory responses, and participate in ALI [59].

LPS in cells will combine with caspase-11 to trigger the oligomerization of caspase-11. The activated caspase-11 will cut down pannexin-1 and open its channel to release ATP, activate P2×7 receptor on the cell surface, regulate the generation and release of caspase-1, induce pyroptosis, and release inflammatory cytokines, thus participating in the occurrence and development of ALI [60, 61] (Fig. 2).

In addition, studies have found that neutrophil pyroptosis, IL-1β and IL-18 can be significantly increased through the NLR Family CARD Domain Containing(NLRC)-4-caspase-1 and NLRP3 caspase-11 pathways, further enhancing the inflammatory response and leading to an increase in the degree of damage to ALI [62] (Fig. 2).

#### Natural killer cell pyroptosis and ALI

Natural killer cell (NK) is the cytotoxic lymphocyte of innate immune system and the most effective immune

cell participating in immune surveillance. It is the first line of defense for the immune system to control pathogens, tumor growth, metastasis and diffusion, accounting for 15% of the resident lung lymphocytes [63]. It can participate in ALI by activating caspase and cleaving GSDMD.

Studies have shown that LPS can bind to TLR4 receptors on the cell membrane, transform pro-caspase-1 into active caspase-1, cut GSDMD into C-terminal and N-terminal, and the active N-terminal polymerizes in the plasma membrane, leading to NK pyroptosis and the secretion of IL-1β, inducing inflammatory reactions and affecting the development process of ALI [64] (Fig. 2).

Another study found that LPS activates caspase-11, and activated caspase-11 cleaves GSDMD, which ultimately induces NK pyroptosis, secretes IL-18, and exacerbates pulmonary inflammation [65].

#### Monocyte pyroptosis and ALI

Monocytes participate in the coordination between innate immunity and adaptive immunity. As the first line of defense of the human body, they can eliminate pathogens through phagocytosis or release inflammatory mediators [66].

Studies have shown that monocytes stimulated by LPS activate NLRP3 inflammasomes, thereby activating caspase-1, which then cleaves GSDMD. Its N-terminal binds to phospholipids in the plasma membrane to form membrane pores and secrete IL-1β, enhance pulmonary inflammation, thereby exacerbating the condition of ALI [67, 68] (Fig. 2).

#### Dendritic cell pyroptosis and ALI

Dendritic cells (DCs) can coordinate and regulate adaptive immune responses, as well as secrete pro-inflammatory cytokines. They are considered the most effective antigen presenting cells [69, 70].

Relevant experiments have proved that LPS can activate TLR4 in dendritic cells, induce its dimerization and endocytosis, activate NLRP3 inflammasome, thus activate caspase-1, cut GSDMD, and its active N-terminal oligomers in the plasma membrane and forms a hole, leading to DC pyroptosis, and eventually secretes the inflammatory cytokines IL-1β and IL-18, which enhances the inflammatory response and ultimately exacerbates the severity of ALI [71, 72] (Fig. 2).

#### Other pyroptosis and ALI

In addition to immune pyroptosis participating in the occurrence and development of ALI, it is also found that endothelial pyroptosis also participates in ALI.

LPS upregulates the expression of caspase-4 in endothelial cells through TLR11, thereby inducing endothelial pyroptosis. Furthermore, the activation of caspase-4 can also be induced by LPS stimulating TLR4-NLRP3 signaling pathway [73] (Fig. 2).

In addition, it was found that the removal of caspase-4 or caspase-5 by siRNA could prevent LPS induced endothelial pyroptosis. Similarly, caspase-11 deficiency prevented an increase in the lung wet/dry weight ratio in ALI mice. Experimental results using lethal LPS doses showed an increased survival rate in caspase-11 deficient mice [46]. Therefore, the above experimental results demonstrate that caspase-11 plays a central role in the LPS induced pyroptosis mechanism of endothelial cells, which is the reason for pulmonary vascular high permeability and mortality. Pulmonary endothelial dysfunction caused by extensive endothelial pyroptosis is also regarded as a sign of ALI [74].

### Mitochondrial dysfunction induces pyroptosis to participate in ALI

In recent years, a great number of studies have found that mitochondrial dysfunction can induce pyroptosis by stimulating inflammatory signaling pathways, secreting inflammatory cytokines and other ways, thus participating in the occurrence and development of ALI. Among them, related mitochondrial dysfunction mainly includes TCA, OXPHOS, ETC, and imbalance of $Ca^{2+}$ homeostasis.

#### Mechanism of pyroptosis induced by disturbance of tricarboxylic acid circulation

The research found that the disorder of TCA induced pyroptosis through oxidative stress, secreted relevant inflammatory cytokines, and participated in ALI.

When the circulation of tricarboxylic acid is impaired, it will induce the dissolution of glial cells, trigger the activation of inflammasome and induce pyroptosis in macrophages. It has been found that the knockout of glutamate pyruvate transaminase (GPT2) will promote the polarization of macrophages to M1 type. When the reaction substrate catalyzed by GPT2 is glutamine, its product is α-KG, which is a metabolite in the TCA, will be reduced to L-2HG by metabolic enzyme malate dehydrogenase in the TCA under acidic conditions, which will increase ROS to induce the internalization of plasma membrane death receptor (DR) 6, further recruit pro-caspase-8 and GSDMC into DR6 receptor, providing a platform for caspase-8 to cut GSDMC, and then induce macrophage pyroptosis, H&E staining showed inflammatory cell infiltration, pulmonary edema, and alveolar collapse [75–77] (Fig. 3).

The above research is only limited to the effect of TCA on the occurrence and development of ALI by inducing macrophage pyroptosis, while mechanism between dendritic cells and other immune pyroptosis and this function has not been studied.

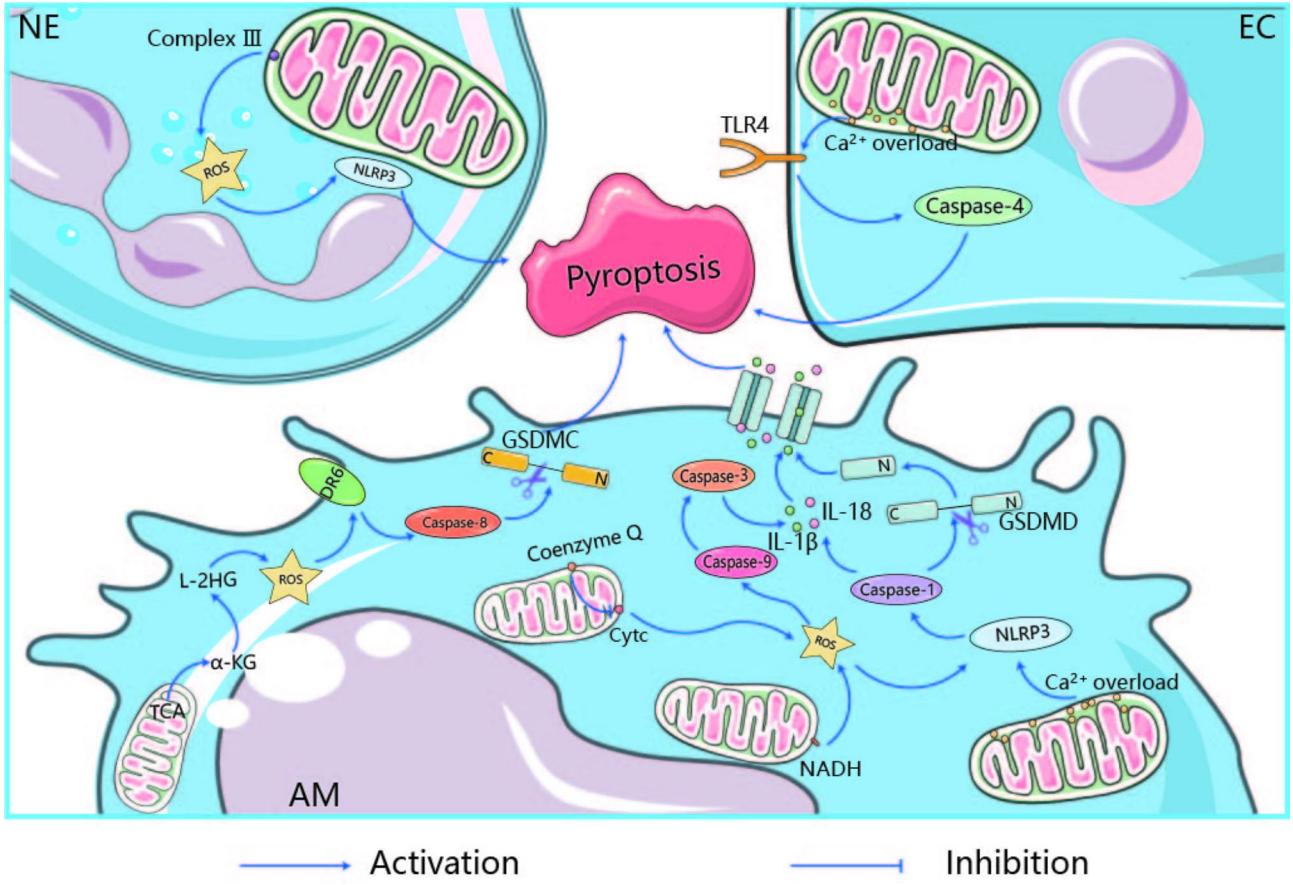


**Fig. 3** The mechanism of mitochondrial dysfunction and pyroptosis. Mechanism of TCA inducing pyroptosis: metabolites α-KG under acidic conditions, will be reduced to L-2HG, increase ROS to induce DR6 internalization, activate caspase-8 and cut GSDMC to induce macrophage pyroptosis. The dysfunction of OXPHOS participates in the mechanism of pyroptosis: the activity of coenzyme Q is inhibited, the release of cytochrome c is promoted, the production of ROS in macrophages is increased, caspase-3 and caspase-9 are activated, the activation of NLRP3 is enhanced, and the expression of IL-1β is increased. The mechanism of ETC disorder involved in pyroptosis: NADH activity was inhibited, increased ROS production, activated NLRP3/caspase-1, cut GSDMD, induced macrophage pyroptosis, and secreted IL-1β. Furthermore, in neutrophils, the activity of mitochondrial complex III is inhibited, which increases the production of ROS, thus activating NLRP3 and inducing pyroptosis. The mechanism of $Ca^{2+}$ dysfunction inducing pyroptosis: $Ca^{2+}$ overload activates NLRP3 /caspase-1, causes macrophage pyroptosis and secretes IL-1β, IL-18. In addition, $Ca^{2+}$ overload also activates TLR4 /caspase-4, leading to endothelial pyroptosis

### Oxidative phosphorylation dysfunction participates in the mechanism of pyroptosis

OXPHOS is involved in ALI through related enzymes and proteins that induce pyroptosis and stimulate the release of inflammatory cytokines such as IL-1β.

The dysfunction of OXPHOS will up regulate the expression of related proteins such as NDUFB3, NDUFB8, ATP5B, etc. Leading to a significant increase in the expression of mtROS and activation of inflammasome NLRP3 [78, 79]. NLRP3 activates caspase-1, converting inactive IL-1β and IL-18 cut into active IL-1β and IL-18, thereby amplifying the inflammatory reaction, leading to highly inflammatory cell death, that is, pyroptosis, and aggravating ALI pulmonary inflammation [80].

Mitochondrial coenzyme Q, a lipid soluble membrane component, exists in the inner mitochondrial membrane of cells and participates in OXPHOS [81]. Coenzyme Q activity is inhibited, which can promote the release of Cytc, increase ROS production in LPS treated macrophages, and activate caspase-3 and caspase-9, significantly enhancing the activation of NLRP3 inflammasomes, thereby significantly increasing the expression of pro-inflammatory cytokines IL-1β and IL-6 levels [82, 83]. (Fig. 3) Further studies have shown that after coenzyme Q treatment, the wet/dry weight (W/D) ratio of lung tissue in LPS-induced acute lung injury rats is significantly reduced, which alleviates pulmonary edema and reduces the expression levels of related pro-inflammatory cytokines such as IL-6, indicating that this enzyme can also reduce inflammatory responses in ALI [84].

At present, the research only focuses on the effect of macrophage charring induced by oxidative phosphorylation dysfunction on ALI, while mechanism between

other immune pyroptosis such as natural killer cell and this function remains to be studied.

### Electron transport chain disorder participates in the mechanism of pyroptosis

The ETC disorder induces pyroptosis by activating relevant inflammatory signal pathways, stimulating relevant protein of pyroptosis, etc., producing inflammatory response and participating in ALI.

Ubiquinone oxidoreductase complex I (NADH) is the first enzyme in the ETC and the key factor for the production of steady-state ROS. When its activity is inhibited, it will lead to the increase of ROS production, activation of NLRP3 and caspase-1, thus cutting GSDMD, and eventually inducing pyroptosis in macrophage and secretion of IL-1β [85–88]. (Fig. 3) In which, NADPH oxidase can oxidize NADPH to produce superoxide, when the ETC dysfunction and NADPH oxidase overexpression, the ROS expression level will increase. Increased alveolar cell death was found by tunel fluorescent staining [89, 90]. Correspondingly, experiments have shown that when cytosine at position 5178 in the DNA sequence of mitochondrial NADH dehydrogenase subunit 2 is replaced by adenine, it increases the stability of the ETC system complex, thereby increasing ATP synthesis and reducing ROS generation [91].

When the activity of mitochondrial complex III is inhibited, the production of ROS in neutrophils is increased, thus activating NLRP3 and inducing pyroptosis [92] (Fig. 3).

After ETC is disrupted, electrons cannot be transferred from complex I or complex II to complex IV through complex III, resulting in an increase in ROS production and activation of more NLRP3, thereby activating caspase-1, cleaving GSDMD protein. It induces pyroptosis and promotes the release of IL-1β and IL-18, which leads to inflammatory cascade and aggravates ALI [93, 94].

Cytc is involved in cellular respiration. It is the electron carrier of complexes III and IV, and forms an ETC with other oxidases at the mitochondrial crest [95]. Cytc combines with apoptotic protein activating factor 1 (Apaf-1) to form a complex, cleaves pro-caspase-9, thus activating caspase-9, and then activates caspase-3, while GSDME is specifically cut and activated by caspase-3, finally inducing pyroptosis. H&E staining revealed a thickened alveolar septa, and an increased number of neutrophils in the interstitial gap [96, 97].

At present, the study on the relationship between ETC dysfunction and immune pyroptosis only focuses on macrophages and neutrophils, while the study on other immune cells is still lacking.

### Mechanism of pyroptosis induced by abnormal Ca2+ steady-state imbalance

After the imbalance of $Ca^{2+}$ homeostasis, pyroptosis is induced by activating inflammatory proteins and pyroptosis related enzymes, secreting inflammatory cytokines, causing inflammatory response, and participating in ALI.

The overload of calcium ions in mitochondria will activate the inflammasome NLRP3, and then activate caspase-1, which will lead to the pyroptosis of macrophages, and finally lead to IL-1β and IL-18 was cut and matured [98–100]. In addition, calcium overload can also activate the TLR4 receptor, thereby activating caspase-4 and leading to endothelial cell pyroptosis, and it leads to increased permeability of pulmonary microvascular endothelial cells, inducing ALI [28] (Fig. 3).

However, there is still a lack of research on dendritic cells, natural killer cell, monocytes and other immune cells due to pyroptosis induced by dysfunction of $Ca^{2+}$.

## Treatment of pyroptosis induced by mitochondrial dysfunction

Mitochondrial dysfunction and pyroptosis play an indispensable role in the occurrence and development of ALI. Factors related to mitochondrial dysfunction and related molecular proteins in the process of pyroptosis may be potential therapeutic targets for ALI.

### The therapy of mitochondrial function

Improving mitochondrial function can reduce the severity of ALI. FuC et al. found that dexmedetomidine (DEX) alleviates LPS induced ALI by improving oxidative stress and mitochondrial dysfunction. The experimental results show that DEX inhibits the generation of ROS after LPS stimulation, and effectively inhibits histopathology changes such as alveolar wall thickening, edema, inflammatory cell infiltration, furthermore, it also prevents excessive vascular permeability [101]. (Table 1) Li W et al. found that oxaloacetic acid treatment of ALI effectively reduces the accumulation of ROS, significantly reduces the expression of malondialdehyde (MDA), and significantly increases the expression of superoxide dismutase (SOD), thereby alleviating cell oxidative stress. And the mRNA expression of peroxisome proliIorators-activated receptor γ coactivator 1 alpha(PGC-1α) and cyclooxygenase-2 (COX-2) are significantly increased, improving mitochondrial respiratory function and enhancing biogenesis and energy metabolism in damaged cells [102]. (Table 1) HeW et al. found that Liangge Tang increased the expression level of α-KG in TCA, thereby inhibiting the activation of NF- κB to inhibit macrophage conversion to M1 type and reduce the release of inflammatory cytokine IL-1β and reduce pulmonary inflammation [103]. (Table 1) For the ETC process, the application of melatonin prevents the inhibition of mitochondrial

**Table 1** Examples of acute lung injury treated by mitochondrial function or pyroptosis

| Treatment | Classification | Specific examples | References |
|---|---|---|---|
| Improve mitochondrial dysfunction | Improve the oxidative phosphorylation | Dexmedetomidine, AdMsc-EXOS | [101] [105] |
| | Improving tricarboxylic acid cycle | Oxaloacetic acid, Liang-Ge decoction | [102] [103] |
| | Improving electronic transmission chain | Melatonin | [104] |
| Decrease pyroptosis | Decrease macrophage pyroptosis | Ligustrazine, Tetracycline, Dexamethasone | [109] [106] [107] |
| | Decrease endothelial pyroptosis | Hepatocyte growth factor | [110] |

complexes I and IV in ALI and improves the generation of mitochondrial ATP [104]. (Table 1) Recovery of OXPHOS function can also improve the extent of ALI damage. After application of adipose derived mesenchymal stem cell derived exosomes (AdMSC Exos), it can reduce the production of ROS in mitochondria, increase the activity of OXPHOS, and reduce the expression of IL-1β and TNF-α after LPS stimulation, ultimately reducing pulmonary inflammatory response [105] (Table 1).

To sum up, the lung damage of ALI can be improved by alleviating the dysfunction of TCA, ETC and OXPHOS, thereby reducing oxidative stress, inflammatory cytokines release, etc., but there is no drug to treat ALI with $Ca^{2+}$ homeostasis, which can be used as a potential therapeutic approach.

#### Treatments of pyroptosis

It is found that inhibiting pyroptosis and reducing the secretion of inflammatory cytokines can participate in the treatment of ALI.

Konrad Peukert et al. found that treatment of ALI with tetracycline reduced the accumulation of protein, albumin and neutrophils in bronchoalveolar lavage fluid, namely effective relief of ALI. Immunoblot analyses showed that tetracycline reduced cleavage and activation of the p45 caspase-1 precursor into its p20 subunit in a dose-dependent fashion, thereby inhibiting the conversion of pro-IL-18 and pro-IL-1β to IL-18 and IL-1β. Furthermore, tetracycline significantly inhibited pyroptosis, which was manifested by reduced lactate dehydrogenase(LDH) release [106]. (Table 1) Yang et al. treated ALI with dexamethasone and found that disruption of alveolar structures and reduced infiltration of inflammatory cells in the lung tissue. Results from flow cytometry and confocal microscopy showed that dexamethasone negatively regulated NLRP3 inflammasome activation by inhibiting NF-κB signaling pathway and mtROS production. Western blot showed that the activation affected caspase-1, prevented the transcription of IL-1β and IL-18, decreased secretion of inflammatory cytokines, and significantly decreased LDH expression. Ultimately play a protective role in inflammation induced by LPS-induced ALI [107]. (Table 1) Jiang et al. found that TMP could inhibit the expression of TLR4 and TRAF6 as upstream molecules, and then prevent the phosphorylation of NF-κB p65 transcription factors into the nucleus to reduce the expression of NLRP3, inhibit the formation of inflammasome complex, reduce the lysis of caspase-1, and lead to reduced macrophage pyroptosis. In addition, when IL-1β and IL-18 are cut and activated by caspase-1, they can be released outside the cell, so the release of inflammatory cytokines was correspondingly reduced [108]. Among them, H&E staining found that it could effectively relieve pulmonary interstitial edema and hemorrhage, alveolar wall thickness and inflammatory cell infiltration caused by LPS [109]. (Table 1) In addition, Peng F et al. found through experiments that high expression of hepatocyte growth factor (HGF) can avoid the disruption of high permeability and integrity of lung endothelial cell monolayer induced by LPS, thereby reducing the degree of ALI damage caused by LPS tracheal infusion. In addition, after intravenous injection of recombinant HGF, the expression of caspase-1 and GSDMD decreased. Flow cytometry and immunofluorescence results showed that mitochondrial integrity was protected, and the ROS produced by endothelial pyroptosis was reduced [110] (Table 1).

At present, there are only specific drug researches on macrophages, while the therapeutic mechanism of other drugs that inhibit neutrophils and other immune pyroptosis on ALI remains to be studied.

#### Combined treatment approach

Studies have shown that mitochondrial targeted antioxidants reducing the ROS produced by LPS stimulation and increased ATP production and mitochondrial membrane potential, it protected the mitochondrial function. The mitochondrial targeted antioxidants increase the expression of the anti-apoptotic factor Bcl-2 and that of the pro-apoptotic factor BAK, which would decrease the permeability of the mitochondrial outer membrane, further reduce Cytc release from mitochondria and inhibit the caspase cascade, reducing the activity of caspase-3 and thereby inhibiting pyroptosis. Moreover, the results of lung histopathological examination showed that the mitochondrial targeted antioxidants group could

significantly improve lung inflammation during ALI, including interstitial edema, congestion and infiltration of inflammatory cells into the lung parenchyma and alveolar spaces [111].

## Conclusion and prospects

The pyroptosis induced by mitochondrial dysfunction plays an important role in the process of ALI. When the dysfunction of TCA, OXPHOS, ETC and $Ca^{2+}$ homeostasis occurs, it will induce immune cells such as macrophages, natural killer cell to produce pyroptosis and release inflammatory cytokines, induce a series of inflammatory reactions, and ultimately promote the occurrence of ALI or aggravate the degree of lung injury.

At present, mitochondrial functional therapy mainly focuses on alleviating the TCA, OXPHOS, ETC dysfunction, inhibiting inflammatory signal pathways, reducing the release of inflammatory cytokines and other mechanisms, but has not specifically involved improving $Ca^{2+}$ homeostasis to play a role. On the other hand, it is to reduce macrophage pyroptosis, alleviate pulmonary inflammation by reducing inflammatory cytokines, and has not yet reduced the pyroptosis of dendritic cells, natural killer cell and other immune pyroptosis to treat ALI.

It may provide a new therapeutic direction and target for clinical prevention and treatment of ALI to reduce pyroptosis by improving mitochondrial dysfunction.

In addition, it was also found that mitochondrial dynamics, such as improving fusion and reducing fission, participated in the treatment of ALI by reducing the secretion of inflammatory cytokines and alleviating oxidative stress damage, and it was also found that it can induce immune pyroptosis, so the mechanism of pyroptosis induced by mitochondrial dynamics in ALI could also be studied in the future.

**Acknowledgements**
Not applicable.

**Author contributions**
ZZ, LY, XJ, and HL contributed to the conception and design of the study. QR and YW performed the statistical analysis. LY wrote the first draft of the manuscript. QR, YW, YZ, FD, FW, JZ, LG, SC, XC, WZ, YS and XZ wrote sections of the manuscript. All authors read and approved the final manuscript.

**Funding**
This project is supported by Sichuan Science and Technology Program (2022YFS0633).

**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

Received: 1 April 2024 / Accepted: 25 October 2024
Published online: 07 November 2024

**References**

1. Peritore AF, D'Amico R, Siracusa R, Cordaro M, Fusco R, Gugliandolo E, et al. Management of acute lung injury: palmitoylethanolamide as a new approach. Int J Mol Sci. 2021;22(11).
2. Zheng Y, Huang Y, Xu Y, Sang L, Liu X, Li Y. Ferroptosis, pyroptosis and necroptosis in acute respiratory distress syndrome. Cell Death Discov. 2023;9(1):91.
3. An N, An J, Zeng T, Wang S, Li P, Hu X, Shen Y, Liu L, Wen F. Research progress of mitochondria in chronic obstructive pulmonary disease: a bibliometric analysis based on the web of Science Core Collection. J Thorac Dis. 2024;16(1):215–30.
4. Ma A, Feng Z, Li Y, Wu Q, Xiong H, Dong M, Cheng J, Wang Z, Yang J, Kang Y. Ferroptosis-related signature and immune infiltration characterization in acute lung injury/acute respiratory distress syndrome. Respir Res. 2023;24(1):154.
5. Mokrá D. Acute lung injury - from pathophysiology to treatment. Physiol Res. 2020;69(Suppl 3):S353–66.
6. Spadaro S, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, Ragazzi R, Ruggeri P, Hansel TT, Caramori G, Volta CA. Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. J Inflamm (Lond). 2019;16:1.
7. Zhang J, Guo Y, Mak M, Tao Z. Translational medicine for acute lung injury. J Transl Med. 2024;22(1):25.
8. Zhou X, Jin J, Lv T, Song Y, Narrative Review A. The role of NETs in acute respiratory distress syndrome/acute lung injury. Int J Mol Sci. 2024;25(3).
9. Liu C, Xiao K, Xie L. Advances in the use of exosomes for the treatment of ALI/ARDS. Front Immunol. 2022;13:971189.
10. Liaqat A, Mason M, Foster BJ, Kulkarni S, Barlas A, Farooq AM, et al. Evidence-based mechanical ventilatory strategies in ARDS. J Clin Med. 2022;11(2).
11. Lee J, Corl K, Levy MM. Fluid therapy and Acute Respiratory Distress Syndrome. Crit Care Clin. 2021;37(4):867–75.
12. Battaglini D, Fazzini B, Silva PL, Cruz FF, Ball L, Robba C, et al. Challenges in ARDS definition, management, and identification of effective personalized therapies. J Clin Med. 2023;12(4).
13. Younes N, Zhou L, Amatullah H, Mei SHJ, Herrero R, Lorente JA, Stewart DJ, Marsden P, Liles WC, Hu P, Dos Santos CC. Mesenchymal stromal/stem cells modulate response to experimental sepsis-induced lung injury via regulation of miR-27a-5p in recipient mice. Thorax. 2020;75(7):556–67.
14. Zhuang X, Jiang Y, Yang X, Fu L, Luo L, Dong Z, Zhao J, Hei F. Advances of mesenchymal stem cells and their derived extracellular vesicles as a promising therapy for acute respiratory distress syndrome: from bench to clinic. Front Immunol. 2023;14:1244930.
15. Jiang S, Nandy P, Wang W, Ma X, Hsia J, Wang C, Wang Z, Niu M, Siedlak SL, Torres S, Fujioka H, Xu Y, Lee HG, Perry G, Liu J, Zhu X. Mfn2 ablation causes an oxidative stress response and eventual neuronal death in the hippocampus and cortex. Mol Neurodegener. 2018;13(1):5.
16. He M, Xiang Z, Xu L, Duan Y, Li F, Chen J. Lipopolysaccharide induces human olfactory ensheathing glial apoptosis by promoting mitochondrial dysfunction and activating the JNK-Bnip3-Bax pathway. Cell Stress Chaperones. 2019;24(1):91–104.
17. Pokharel MD, Garcia-Flores A, Marciano D, Franco MC, Fineman JR, Aggarwal S, Wang T, Black SM. Mitochondrial network dynamics in pulmonary disease: bridging the gap between inflammation, oxidative stress, and bioenergetics. Redox Biol. 2024;70:103049.
18. Soubannier V, McLelland GL, Zunino R, Braschi E, Rippstein P, Fon EA, McBride HM. A vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Curr Biol. 2012;22(2):135–41.
19. Soubannier V, Rippstein P, Kaufman BA, Shoubridge EA, McBride HM. Reconstitution of mitochondria derived vesicle formation demonstrates selective enrichment of oxidized cargo. PLoS One. 2012;7(12):e52830.
20. Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, Suomalainen A, Thorburn DR, Zeviani M, Turnbull DM. Mitochondrial diseases. Nat Rev Dis Primers. 2016;2:16080.
21. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, Luque-Martin R, Chen HJ, Boshuizen MC, Ahmed M, Hoeksema MA,

de Vos AF, de Winther MP. Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. Cell Rep. 2016;17(3):684–96.
22. Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, Tourlomousis P, Däbritz JHM, Gottlieb E, Latorre I, Corr SC, McManus G, Ryan D, Jacobs HT, Szibor M, Xavier RJ, Braun T, Frezza C, Murphy MP, O'Neill LA. Succinate dehydrogenase supports metabolic repurposing of Mitochondria to Drive Inflammatory macrophages. Cell. 2016;167(2):457–e47013.
23. Lu JW, Zhai YJ, Sun F. Advances in research on mitochondrial calcium ion transport. Acta Biophys Sinica. 2013;29:167–80.
24. Tao X, Wei LB, Guo LQ. Research progress on the role and mechanism of mitochondrial calcium ions in regulating tumor development. World Med Inform Digest. 2020;20(26):83–8588.
25. Mason FE, Pronto JRD, Alhussini K, Maack C, Voigt N. Cellular and mitochondrial mechanisms of atrial fibrillation. Basic Res Cardiol. 2020;115(6):72.
26. Schappe MS, Szteyn K, Stremska ME, Mendu SK, Downs TK, Seegren PV, Mahoney MA, Dixit S, Krupa JK, Stipes EJ, Rogers JS, Adamson SE, Leitinger N, Desai BN. Chanzyme TRPM7 mediates the ca(2+) influx essential for Lipopolysaccharide-Induced Toll-Like receptor 4 endocytosis and macrophage activation. Immunity. 2018;48(1):59–e745.
27. Li C, Bo L, Liu Q, Liu W, Chen X, Xu D, Jin F. Activation of TRPV1-dependent calcium oscillation exacerbates seawater inhalation-induced acute lung injury. Mol Med Rep. 2016;13(3):1989–98.
28. Hao Y, Wang Z, Frimpong F, Chen X. Calcium-permeable channels and endothelial dysfunction in Acute Lung Injury. Curr Issues Mol Biol. 2022;44(5):2217–29.
29. Calì T, Ottolini D, Brini M. Mitochondrial ca(2+) and neurodegeneration. Cell Calcium. 2012;52(1):73–85.
30. Kogot-Levin A, Saada A. Ceramide and the mitochondrial respiratory chain. Biochimie. 2014;100:88–94.
31. Jiang X, Li L, Ying Z, Pan C, Huang S, Li L, Dai M, Yan B, Li M, Jiang H, Chen S, Zhang Z, Wang X. A small molecule that protects the Integrity of the Electron transfer Chain blocks the mitochondrial apoptotic pathway. Mol Cell. 2016;63(2):229–39.
32. Ghanizadeh A, Berk M, Farrashbandi H, Alavi Shoushtari A, Villagonzalo KA. Targeting the mitochondrial electron transport chain in autism, a systematic review and synthesis of a novel therapeutic approach. Mitochondrion. 2013;13(5):515–9.
33. Song Y, Pinniger GJ, Bakker AJ, Moss TJ, Noble PB, Berry CA, et al. Lipopolysaccharide-induced weakness in the preterm diaphragm is associated with mitochondrial electron transport chain dysfunction and oxidative stress. PLoS One. 2013;8(9):e73457.
34. Zamani E, Shaki F, AbedianKenari S, Shokrzadeh M. Acrylamide induces immunotoxicity through reactive oxygen species production and caspase-dependent apoptosis in mice splenocytes via the mitochondria-dependent signaling pathways. Biomed Pharmacother. 2017;94:523–30.
35. Sun H, Zhao ZG, Li SG. The role of reactive oxygen species in acute lung injury induced by hemorrhagic shock. Chin Emerg Med. 2017;37:92–6.
36. Pala R, Orhan C, Tuzcu M, Sahin N, Ali S, Cinar V, Atalay M, Sahin K. Coenzyme Q10 Supplementation modulates NFκB and Nrf2 pathways in Exercise Training. J Sports Sci Med. 2016;15(1):196–203.
37. Lee IT, Yang CM. Role of NADPH oxidase/ROS in pro-inflammatory mediators-induced airway and pulmonary diseases. Biochem Pharmacol. 2012;84(5):581–90.
38. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Siegal GP, Abraham E. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. Am J Respir Crit Care Med. 2008;178(2):168–79.
39. Dhlamini Q, Wang W, Feng G, Chen A, Chong L, Li X, Li Q, Wu J, Zhou D, Wang J, Zhang H, Zhang JS. FGF1 alleviates LPS-induced acute lung injury via suppression of inflammation and oxidative stress. Mol Med. 2022;28(1):73.
40. van der Bliek AM, Sedensky MM, Morgan PG. Cell Biology of the Mitochondrion. Genetics. 2017;207(3):843–71.
41. Navas LE, Carnero A. NAD(+) metabolism, stemness, the immune response, and cancer. Signal Transduct Target Ther. 2021;6(1):2.
42. Hooftman A, Angiari S, Hester S, Corcoran SE, Runtsch MC, Ling C, Ruzek MC, Slivka PF, McGettrick AF, Banahan K, Hughes MM, Irvine AD, Fischer R, O'Neill LAJ. The Immunomodulatory Metabolite Itaconate modifies NLRP3 and inhibits inflammasome activation. Cell Metab. 2020;32(3):468–e4787.
43. Liu M, Chen Y, Wang S, Zhou H, Feng D, Wei J, Shi X, Wu L, Zhang P, Yang H, Lv X. α-Ketoglutarate modulates macrophage polarization through regulation of PPARγ transcription and mTORC1/p70S6K pathway to Ameliorate ALI/ARDS. Shock. 2020;53(1):103–13.
44. Yadav H, Thompson BT, Gajic O. Fifty years of Research in ARDS. Is Acute Respiratory Distress Syndrome a Preventable Disease? Am J Respir Crit Care Med. 2017;195(6):725–36.
45. Wu DD, Pan PH, Liu B. Inhibition of alveolar macrophage pyroptosis reduces lipopolysaccharide-induced Acute Lung Injury in mice. Chin Med J (Engl). 2015;128(19):2638–45.
46. Cheng KT, Xiong S, Ye Z, Hong Z, Di A, Tsang KM, Gao X, An S, Mittal M, Vogel SM, Miao EA, Rehman J, Malik AB. Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. J Clin Invest. 2017;127(11):4124–35.
47. Kojima M, Gimenes-Junior JA, Chan TW, Eliceiri BP, Baird A, Costantini TW, Coimbra R. Exosomes in postshock mesenteric lymph are key mediators of acute lung injury triggering the macrophage activation via toll-like receptor 4. Faseb j. 2018;32(1):97–110.
48. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, Locati M, Mantovani A, Martinez FO, Mege JL, Mosser DM, Natoli G, Saeij JP, Schultze JL, Shirey KA, Sica A, Suttles J, Udalova I, van Ginderachter JA, Vogel SN, Wynn T. A., macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014;41(1):14–20.
49. Hung CM, Peng CK, Wu CP, Huang KL. Bumetanide attenuates acute lung injury by suppressing macrophage activation. Biochem Pharmacol. 2018;156:60–7.
50. Xu P, Wen Z, Shi X, Li Y, Fan L, Xiang M, Li A, Scott MJ, Xiao G, Li S, Billiar TR, Wilson MA, Fan J. Hemorrhagic shock augments Nlrp3 inflammasome activation in the lung through impaired pyrin induction. J Immunol. 2013;190(10):5247–55.
51. Jiang Q, Zhang WK. Research progress on the mechanism of acute lung injury induced by lipopolysaccharide and the protective effect of reduced glutathione. Chin J Clin Physicians. 2017;11(04):645–9.
52. Hou L, Yang Z, Wang Z, Zhang X, Zhao Y, Yang H, Zheng B, Tian W, Wang S, He Z, Wang X. NLRP3/ASC-mediated alveolar macrophage pyroptosis enhances HMGB1 secretion in acute lung injury induced by cardiopulmonary bypass. Lab Invest. 2018;98(8):1052–64.
53. Wang J, Li R, Peng Z, Hu B, Rao X, Li J. [Corrigendum] HMGB1 participates in LPS–induced acute lung injury by activating the AIM2 inflammasome in macrophages and inducing polarization of M1 macrophages via TLR2, TLR4, and RAGE/NF–κB signaling pathways. Int J Mol Med. 2020;45(5):1628.
54. He X, Qian Y, Li Z, Fan EK, Li Y, Wu L, Billiar TR, Wilson MA, Shi X, Fan J. TLR4-Upregulated IL-1β and IL-1RI promote alveolar macrophage pyroptosis and lung inflammation through an Autocrine mechanism. Sci Rep. 2016;6:31663.
55. Kantari C, Pederzoli-Ribeil M, Witko-Sarsat V. The role of neutrophils and monocytes in innate immunity. Contrib Microbiol. 2008;15:118–46.
56. Borregaard N, Theilgaard-Mönch K, Cowland JB, Ståhle M, Sørensen OE. Neutrophils and keratinocytes in innate immunity–cooperative actions to provide antimicrobial defense at the right time and place. J Leukoc Biol. 2005;77(4):439–43.
57. Li H, Zhou X, Tan H, Hu Y, Zhang L, Liu S, Dai M, Li Y, Li Q, Mao Z, Pan P, Su X, Hu C. Neutrophil extracellular traps contribute to the pathogenesis of acid-aspiration-induced ALI/ARDS. Oncotarget. 2018;9(2):1772–84.
58. Li H, Li Y, Song C, Hu Y, Dai M, Liu B, Pan P. Neutrophil Extracellular traps augmented alveolar macrophage pyroptosis via AIM2 inflammasome activation in LPS-Induced ALI/ARDS. J Inflamm Res. 2021;14:4839–58.
59. Burdette BE, Esparza AN, Zhu H, Wang S. Gasdermin D in pyroptosis. Acta Pharm Sin B. 2021;11(9):2768–82.
60. Liu L, Sun B. Neutrophil pyroptosis: new perspectives on sepsis. Cell Mol Life Sci. 2019;76(11):2031–42.
61. Li N, Jia J, Wu X, Zhao Y, Zang B. [Regulatory effect of hemichannels protein Pannexin-1 on P2X7 receptor activity in the lungs of mice with lung injury]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2018;30(11):1071–6.
62. Ryu JC, Kim MJ, Kwon Y, Oh JH, Yoon SS, Shin SJ, Yoon JH, Ryu JH. Neutrophil pyroptosis mediates pathology of P. Aeruginosa lung infection in the absence of the NADPH oxidase NOX2. Mucosal Immunol. 2017;10(3):757–74.
63. Federici C, Shahaj E, Cecchetti S, Camerini S, Casella M, Iessi E, Camisaschi C, Paolino G, Calvieri S, Ferro S, Cova A, Squarcina P, Bertuccini L, Iosi F, Huber V, Lugini L. Natural-killer-derived extracellular vesicles: Immune sensors and interactors. Front Immunol. 2020;11:262.
64. Muhammad JS, Jayakumar MN, Elemam NM, Venkatachalam T, Raju TK, Hamoudi RA, Maghazachi AA. Gasdermin D hypermethylation inhibits pyroptosis and LPS-Induced IL-1β release from NK92 cells. Immunotargets Ther. 2019;8:29–41.

65. Kovacs SB, Oh C, Maltez VI, McGlaughon BD, Verma A, Miao EA, Aachoui Y. Neutrophil Caspase-11 is essential to defend against a cytosol-invasive bacterium. Cell Rep. 2020;32(4):107967.
66. Gren ST, Grip O. Role of monocytes and Intestinal macrophages in Crohn's Disease and Ulcerative Colitis. Inflamm Bowel Dis. 2016;22(8):1992–8.
67. Netea MG, Nold-Petry CA, Nold MF, Joosten LA, Opitz B, van der Meer JH, van de Veerdonk FL, Ferwerda G, Heinhuis B, Devesa I, Funk CJ, Mason RJ, Kullberg BJ, Rubartelli A, van der Meer JW, Dinarello CA. Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages. Blood. 2009;113(10):2324–35.
68. Sauter KA, Wood LJ, Wong J, Iordanov M, Magun BE. Doxorubicin and daunorubicin induce processing and release of interleukin-1β through activation of the NLRP3 inflammasome. Cancer Biol Ther. 2011;11(12):1008–16.
69. Gardner A, de Mingo Pulido Á, Ruffell B. Dendritic cells and their role in Immunotherapy. Front Immunol. 2020;11:924.
70. Patente TA, Pinho MP, Oliveira AA, Evangelista GCM, Bergami-Santos PC, Barbuto JAM. Human dendritic cells: their heterogeneity and clinical application potential in Cancer Immunotherapy. Front Immunol. 2018;9:3176.
71. Zanoni I, Tan Y, Di Gioia M, Broggi A, Ruan J, Shi J, Donado CA, Shao F, Wu H, Springstead JR, Kagan JC. An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells. Science. 2016;352(6290):1232–6.
72. Wang LX, Ren C, Yao RQ, Luo YN, Yin Y, Wu Y, Dong N, Zhu XM, Yao YM. Sestrin2 protects against lethal sepsis by suppressing the pyroptosis of dendritic cells. Cell Mol Life Sci. 2021;78(24):8209–27.
73. Yang J, Zhao Y, Zhang P, Li Y, Yang Y, Yang Y, et al. Hemorrhagic shock primes for lung vascular endothelial cell pyroptosis: role in pulmonary inflammation following LPS. Cell Death Dis. 2016;7(9):e2363.
74. Liu H, Yu X, Yu S, Kou J. Molecular mechanisms in lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. Int Immunopharmacol. 2015;29(2):937–46.
75. Xia Y, Chen S, Zeng S, Zhao Y, Zhu C, Deng B, et al. Melatonin in macrophage biology: current understanding and future perspectives. J Pineal Res. 2019;66(2):e12547.
76. Park JH, Ku HJ, Lee JH, Park JW. Disruption of IDH2 attenuates lipopolysaccharide-induced inflammation and lung injury in an α-ketoglutarate-dependent manner. Biochem Biophys Res Commun. 2018;503(2):798–802.
77. Zhang JY, Zhou B, Sun RY, Ai YL, Cheng K, Li FN, Wang BR, Liu FJ, Jiang ZH, Wang WJ, Zhou D, Chen HZ, Wu Q. The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. Cell Res. 2021;31(9):980–97.
78. Chung IC, Chen LC, Tsang NM, Chuang WY, Liao TC, Yuan SN, OuYang CN, Ojcius DM, Wu CC, Chang YS. Mitochondrial oxidative phosphorylation Complex regulates NLRP3 inflammasome activation and predicts patient survival in nasopharyngeal carcinoma. Mol Cell Proteom. 2020;19(1):142–54.
79. Sandhir R, Halder A, Sunkaria A. Mitochondria as a centrally positioned hub in the innate immune response. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1090–7.
80. Liao J, Yang F, Tang Z, Yu W, Han Q, Hu L, Li Y, Guo J, Pan J, Ma F, Ma X, Lin Y. Inhibition of caspase-1-dependent pyroptosis attenuates copper-induced apoptosis in chicken hepatocytes. Ecotoxicol Environ Saf. 2019;174:110–9.
81. Lee HJ, Park JH, Hoe HS. Idebenone regulates Aβ and LPS-Induced neurogliosis and cognitive function through inhibition of NLRP3 Inflammasome/IL-1β Axis Activation. Front Immunol. 2022;13:749336.
82. Zhong X, Yi X, da Silveira ESRC, Zhang Y, Liu K, Xiao F, et al. CoQ10 deficiency may indicate mitochondrial dysfunction in cr(VI) toxicity. Int J Mol Sci. 2017;18(4).
83. Hseu YC, Tseng YF, Pandey S, Shrestha S, Lin KY, Lin CW, et al. Coenzyme Q(0) inhibits NLRP3 inflammasome activation through mitophagy induction in LPS/ATP-Stimulated macrophages. Oxid Med Cell Longev. 2022;2022:4266214.
84. Li R, Ren T, Zeng J. Mitochondrial coenzyme Q protects Sepsis-Induced Acute Lung Injury by activating PI3K/Akt/GSK-3β/mTOR pathway in rats. Biomed Res Int. 2019;2019:5240898.
85. Jacquemin G, Margiotta D, Kasahara A, Bassoy EY, Walch M, Thiery J, Lieberman J, Martinvalet D. Granzyme B-induced mitochondrial ROS are required for apoptosis. Cell Death Differ. 2015;22(5):862–74.
86. Ghosh S, Castillo E, Frias ES, Swanson RA. Bioenergetic regulation of microglia. Glia. 2018;66(6):1200–12.
87. Cohen TS, Boland ML, Boland BB, Takahashi V, Tovchigrechko A, Lee Y, Wilde AD, Mazaitis MJ, Jones-Nelson O, Tkaczyk C, Raja R, Stover CK, Sellman BR. Aureus evades macrophage killing through NLRP3-Dependent effects on mitochondrial trafficking. Cell Rep. 2018;22(9):2431–41.
88. Wang Y, Shi P, Chen Q, Huang Z, Zou D, Zhang J, Gao X, Lin Z. Mitochondrial ROS promote macrophage pyroptosis by inducing GSDMD oxidation. J Mol Cell Biol. 2019;11(12):1069–82.
89. Shirmanova MV, Gavrina AI, Kovaleva TF, Dudenkova VV, Zelenova EE, Shcheslavskiy VI, Mozherov AM, Snopova LB, Lukyanov KA, Zagaynova EV. Insight into redox regulation of apoptosis in cancer cells with multiparametric live-cell microscopy. Sci Rep. 2022;12(1):4476.
90. Carnesecchi S, Deffert C, Pagano A, Garrido-Urbani S, Métrailler-Ruchonnet I, Schäppi M, Donati Y, Matthay MA, Krause KH, Barazzone Argiroffo C. NADPH oxidase-1 plays a crucial role in hyperoxia-induced acute lung injury in mice. Am J Respir Crit Care Med. 2009;180(10):972–81.
91. Tian L, Zhu C, Yang H, Li Y, Liu Y. Protective effect of Mitochondrial ND2 C5178A gene mutation on cell and mitochondrial functions. Oxid Med Cell Longev. 2021;2021:4728714.
92. Zmijewski JW, Lorne E, Banerjee S, Abraham E. Participation of mitochondrial respiratory complex III in neutrophil activation and lung injury. Am J Physiol Lung Cell Mol Physiol. 2009;296(4):L624–34.
93. Wei X, Wu Y, Pan H, Zhang Q, He K, Xia G, Xia H, Lin S, Shang HC. Proteomics revealed that mitochondrial function contributed to the Protective Effect of Herba Siegesbeckiae against Cardiac Ischemia/Reperfusion Injury. Front Cardiovasc Med. 2022;9:895797.
94. Deng Y, Xie M, Li Q, Xu X, Ou W, Zhang Y, Xiao H, Yu H, Zheng Y, Liang Y, Jiang C, Chen G, Du D, Zheng W, Wang S, Gong M, Chen Y, Tian R, Li T. Targeting mitochondria-inflammation circuit by β-Hydroxybutyrate mitigates HFpEF. Circ Res. 2021;128(2):232–45.
95. Wang L, Duan Q, Wang T, Ahmed M, Zhang N, Li Y, et al. Mitochondrial respiratory chain inhibitors involved in ROS production induced by acute high concentrations of iodide and the effects of SOD as a protective factor. Oxid Med Cell Longev. 2015;2015:217670.
96. Wang Y, Gao W, Shi X, Ding J, Liu W, He H, Wang K, Shao F. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. Nature. 2017;547(7661):99–103.
97. Sekijima H, Oshima T, Ueji Y, Kuno N, Kondo Y, Nomura S, Asakura T, Sakai-Sugino K, Kawano M, Komada H, Kotani H. Toxicologic pathological mechanism of acute lung injury induced by oral administration of benzalkonium chloride in mice. Toxicol Res. 2023;39(3):409–18.
98. Tian C, Liu Y, Li Z, Zhu P, Zhao M. Mitochondria Related Cell Death modalities and Disease. Front Cell Dev Biol. 2022;10:832356.
99. Fu Q, Wu J, Zhou XY, Ji MH, Mao QH, Li Q, Zong MM, Zhou ZQ, Yang JJ. NLRP3/Caspase-1 Pathway-Induced pyroptosis mediated cognitive deficits in a mouse model of Sepsis-Associated Encephalopathy. Inflammation. 2019;42(1):306–18.
100. Thrum S, Sommer M, Raulien N, Gericke M, Massier L, Kovacs P, Krasselt M, Landgraf K, Körner A, Dietrich A, Blüher M, Rossol M, Wagner U. Macrophages in obesity are characterised by increased IL-1β response to calcium-sensing receptor signals. Int J Obes (Lond). 2022;46(10):1883–91.
101. Fu C, Dai X, Yang Y, Lin M, Cai Y, Cai S. Dexmedetomidine attenuates lipopolysaccharide-induced acute lung injury by inhibiting oxidative stress, mitochondrial dysfunction and apoptosis in rats. Mol Med Rep. 2017;15(1):131–8.
102. Li W, Li M, Chen K, Tang Y, Yin R, Lan L, Hong G. Oxaloacetate acid ameliorates paraquat-induced acute lung injury by alleviating oxidative stress and mitochondrial dysfunction. Front Pharmacol. 2022;13:1029775.
103. He W, Xi Q, Cui H, Zhang P, Huang R, Wang T, Wang D. Liang-Ge decoction ameliorates acute lung injury in septic model rats through reducing inflammatory response, oxidative stress, apoptosis, and modulating host metabolism. Front Pharmacol. 2022;13:926134.
104. Srinivasan V, Mohamed M, Kato H. Melatonin in bacterial and viral infections with focus on sepsis: a review. Recent Pat Endocr Metab Immune Drug Discov. 2012;6(1):30–9.
105. Xia L, Zhang C, Lv N, Liang Z, Ma T, Cheng H, Xia Y, Shi L. AdMSC-derived exosomes alleviate acute lung injury via transferring mitochondrial component to improve homeostasis of alveolar macrophages. Theranostics. 2022;12(6):2928–47.
106. Peukert K, Fox M, Schulz S, Feuerborn C, Frede S, Putensen C, Wrigge H, Kümmerer BM, David S, Seeliger B, Welte T, Latz E, Klinman D, Wilhelm C, Steinhagen F, Bode C. Inhibition of Caspase-1 with tetracycline ameliorates Acute Lung Injury. Am J Respir Crit Care Med. 2021;204(1):53–63.
107. Yang JW, Mao B, Tao RJ, Fan LC, Lu HW, Ge BX, Xu JF. Corticosteroids alleviate lipopolysaccharide-induced inflammation and lung injury via inhibiting NLRP3-inflammasome activation. J Cell Mol Med. 2020;24(21):12716–25.

108. He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, Yang ZH, Zhong CQ, Han J. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Res. 2015;25(12):1285–98.
109. Jiang R, Xu J, Zhang Y, Zhu X, Liu J, Tan Y. Ligustrazine Alleviate Acute Lung Injury through suppressing pyroptosis and apoptosis of alveolar macrophages. Front Pharmacol. 2021;12:680512.
110. Peng F, Chang W, Sun Q, Xu X, Xie J, Qiu H, Yang Y. HGF alleviates septic endothelial injury by inhibiting pyroptosis via the mTOR signalling pathway. Respir Res. 2020;21(1):215.
111. Cen M, Ouyang W, Zhang W, Yang L, Lin X, Dai M, Hu H, Tang H, Liu H, Xia J, Xu F. MitoQ protects against hyperpermeability of endothelium barrier in acute lung injury via a Nrf2-dependent mechanism. Redox Biol. 2021;41:101936.

## Publisher's note