Research Progress on the Pathogenesis of Acute Lung Injury (ALI)

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Abstract In this review, the databases searched were PubMed and Web of Science. It is believed that the main causes of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are inflammatory response disorders, excessive oxidative stress, cell death, endoplasmic reticulum stress, coagulation dysfunction, and weakened aquaporin function.

Key words Acute lung injury (ALI), Pathogenesis, Inflammatory responses, Oxidative stress, Cell death, Endoplasmic reticulum stress, Coagulopathy, Downregulation of aquaporin

1 Introduction

Acute lung injury (ALI) is a clinical syndrome characterized by inflammation and increased pulmonary capillary permeability. In severe cases, it can lead to acute respiratory distress syndrome (ARDS), and ALI/ARDS encompasses a diverse range of pathological processes[1]. The morbidity rates of ALI/ARDS range from 26% to 47%, while the mortality rates are up to 35% -46%[2]. The pathogenesis of ALI/ARDS is a complex and poorly understood process. While treatment methods have improved over time, existing therapeutic approaches and pharmacological therapies have not proven effective in lowering the morbidity and mortality of ARDS patients, which poses a serious threat to human life and health[3]. A review of the literature indicates that the majority of ALI patients can resume to normal or near-normal lung function following treatment. However, they may experience significant and persistent muscle weakness, polyneuropathy, tracheal stenosis, spasticity, and other adverse effects, in addition to a significantly elevated incidence of depression, anxiety, and post-traumatic stress disorder[4]. Therefore, a more profound and comprehensive investigation of the pathogenesis of ALI/ARDS will have a substantial impact on reducing the morbidity and mortality rates among ALI/ARDS patients. In this review, the databases searched were PubMed and Web of Science. It is believed that the main causes of ALI/ARDS are inflammatory response disorders, excessive oxidative stress, cell death, endoplasmic reticulum stress, coagulation dysfunction, and weakened aquaporin function.

2 Inflammatory response disorders

The dysregulated inflammatory response is considered to be the leading etiology of modern ALIs, which are characterized by cytokine storms. These storms are closely linked to immune cells, including neutrophils, macrophages, alveolar epithelial cells (ACEs), natural killer (NK) cells, T cells, and others. They are also linked to cytokines and the complement system[5].

In the inflammatory response of ALI, the complement system is also involved in the generation of cytokine storms[6]. The complement system represents a pivotal component of the innate immune system, comprising proteases, receptors and inhibitors. The complement system's primary functions are the removal of cellular debris, the promotion of inflammation, and the defense against pathogens[7-8]. The complement system activation contributes to the formation of C5b-9 membrane attack complexes, which are capable of destroying the membrane of the target cell, leading to cell lysis and death[9]. Overactivated complement systems play a crucial role in the development of autoimmune diseases, acute inflammatory diseases, and tissue damage[10-11]. Additionally, these pathways facilitate the production of C3a, C3b, C4a, C4a, and C5a. C5a fragments are the primary allergenic toxin that induces the recruitment and activation of neutrophils and macrophages. The C3b fragment is known to stimulate the phagocytosis of neutrophils and macrophages. Furthermore, the C3a, C4a, and C5a fragments can induce the release of inflammatory mediators, including histamine and serotonin, by activating basophils and mast cells[12-14]. The complement system initiates the ALI inflammatory process through both classical and alternative pathways, resulting in the destruction of the endothelium. This, in turn, causes damaged lung cells to release some tissue factors or enzymes, which then initiates the complement cascade, forming a vicious circle of complement activation and lung damage[15]. Studies on alternative complement pathways in critically ARDS patients and murine pneumonia models have found that enhancing the function of alternative complement pathways can enhance host immunity and improve survival during critical illness. One of the mechanisms that HD-PS-3 treats ALI is by reducing the deposition of lung C3c in lung tissue, reducing the content of C3a in BALF, and inhibiting complement activation[16].

After identifying the pathogen, immune cells initiate a cascade of events involving the activation of several signaling path-

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ways, including JAK, protein kinase B (PKB/Akt), MAPKs, IL-1 receptor-associated kinase 1 (IRAK1), and further promote the phosphorylation of STAT and nuclear translocation of NF-κB. The activation of these signaling pathways can upregulate the expression of genes for inflammatory response, and release pro-inflammatory substances such as MPO, MCP-1, IL-6, IL-8, IL-1β, TNF and others[17]. Additionally, pathogens can activate complement to produce protein fragments that exacerbate the inflammatory response. These include IL, TNF and protein fragments produced by the activation of the complement system that bind to relevant receptors on immune cells, leading to the amplification of inflammatory signals and the formation of cytokine storms[17-18]. The cytokine storm results in the destruction of pulmonary capillary endothelial cells and pulmonary epithelial cells, increases the permeability of pulmonary microvessels, microthrombosis, and ultimately leads to damage to alveolar endothelial cells. This damage causes a large amount of protein- and fibrin-rich fluid to leak into the lung matrix and alveoli, forming non-cardiopulmonary edema and opacity[19], decreased lung compliance, persistent hypoxia, reduced Na-K-ATPase activity in alveolar epithelial cells, disturbance of cellular metabolism and further exacerbation of fluid retention and hypoxia, while the inflammatory response is further exacerbated by the activation of oxygen-sensitive proline hydroxylase, ultimately leading to ALI[20].

3 Excessive oxidative stress

Reactive oxygen species (ROS) are produced in the body by aerobic organisms as by-products of energy metabolism through oxidative phosphorylation[21]. Cells typically express several ROS scavengers, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px), as well as the nuclear factor erythro-like 2 correlated factors (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway. These mechanisms serve to prevent free radical damage to biological systems and maintain the balance of the body's oxidative-antioxidant system[22]. Oxidative stress may be the result of an imbalance in the oxidative-antioxidant system, increased production of free radicals, or decreased activity of antioxidant enzymes[23]. Studies have shown that exposure to various stimuli (*e. g.* LPS) results in a reduction in antioxidant enzyme activity and an increase in the levels of reactive oxygen species (ROS), which can lead to damage to the body[24]. An important pathogenic factor in ALI is thought to be excessive oxidative stress. Excessive ROS can reduce membrane fluidity, and increase membrane permeability, resulting in pulmonary edema, and lung dilatation and impairment of endothelial function, thus promoting lung inflammation. Similarly, inflammatory reactions can induce the excessive production of ROS, thereby establishing a vicious cycle of ALI[25]. Studies have demonstrated that Nrf2 scavenges ROS products by regulating antioxidant proteins, indicating that the activation of Nrf2 signaling plays a crucial role in preventing damage to cells and tissues caused by oxidative stress and has a protective effect against several lung diseases, including ALI[26]. HO-1 has been demonstrated to modulate mitochondrial morphology, thereby reducing ROS damage in LPS-induced rat ALI[27]. Therefore, oxidative stress-induced ALI can be mitigated by the activation of Nrf2 and HO-1, accompanied by an increase in the levels of the corresponding antioxidant proteins.

4 Cell death

Cell death is process by which damaged, infected, or degenerated cells are removed, and it is an essential component of homeostasis in multicellular organisms[28]. The primary cause of pathological changes in the lung is cell death in epithelial and endothelial cells. This lung cell death leads to the activation of immune cells, such as lung macrophages, and the release of a variety of pro-inflammatory mediators, which in turn induce inflammatory responses that are closely associated with ALI, including autophagy, cell pyroptosis, apoptosis, and ferroptosis.

4.1 Autophagy Autophagy is an intracellular process that promotes the massive degradation of cytoplasmic materials (such as lipids and misfolded proteins) by vacuoles or lysosomes in eukaryotes. This conserved process is achieved by coordinating the expression of different autophagy-associated genes (ATGs)[29-30]. The term "cell autophagy" encompasses three distinct autophagy pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy[31]. In general, autophagy has two functions. One is an early adaptive mechanism of tissues to remove organelles or proteins to maintain intracellular homeostasis[32]. The other is that excessive autophagy can lead to the death of the autophagic cell[33]. Following the formation of the autophagosome, PI3 kinase (PI3K) complexes generate PI(3)P on the autophagosome membrane, being composed of core components VPS34, VPS15, and Beclin 1[34]. Among them, Beclin 1 is the core involved in autophagy, and its post-translational modifications affect its stability, interaction, and the ability to regulate the activity of PI3K, helping cells fine-tune autophagy[35]. Autophagy has been demonstrated to regulate a number of key processes, including inflammatory oxidative stress, apoptosis, pathogen clearance mechanisms and immune regulation, thereby preventing recurrent pulmonary exacerbations and disease progression, playing a protective role in LPS, sepsis and hyperoxia-induced ALI[36]. In cases of lung injury, key regulators that can influence autophagy include Beclin 1, mTOR, and p62, which occupy a key role in maintaining autophagy's normal function, preventing cell damage, and regulating cell death[37]. Studies have shown that an increase in the number of autophagosomes may offer protection against the effects of LPS-induced ALI in the mouse[38]. Knockdown of GGPPS1 inhibits the activity of the NLRP3 inflammasome by promoting autophagy, thereby attenuating sepsis-induced ALI[39]. Dysfunctional autophagy, however, is the cause of several pathological condi-

tions[40]. The autophagy of alveolar macrophage in LPS-induced ALI has been demonstrated to promote a transition from M2 to M1, thereby enhancing apoptosis[41]. The study has shown that irisin can activate autophagy and restore impaired autophagy flow through the AMPK/mTOR signaling pathway, thereby effectively improving $PM_{2.5}$-induced acute lung injury[42].

4.2 Apoptosis Apoptosis is an active process of cell suicide that maintains normal tissue morphology and function. It is a form of cell death that is genetically controlled according to a specific program, which is the reason for the "programmed cell death". The process of apoptosis is dominated by two main pathways: endogenous apoptosis, which controlled by a balance between members of the different B-cell lymphoma 2 (Bcl2) families, and exogenous apoptosis, which is initiated by members of the tumor necrosis factor superfamily that activate a lethal signaling cascade by binding to cell surface receptors, leading to exogenous apoptosis. All apoptotic pathways are related to cysteine proteins (caspases), and apoptosis of lung cells caused by various environmental stresses (*e. g.* hypoxia, hyperoxia, oxidants, and LPS) can induce ALI[43]. Endogenous apoptosis is one of the causes of endogenous cell suicide, primarily resulting from endoplasmic reticulum (ER) stress[44]. Under normal physiological conditions, the endoplasmic reticulum plays an important role in the storage of calcium (Ca^{2+}), the synthesis of lipids, and the folding and assembly of proteins. In various pathological conditions such as sepsis, trauma, ischemia, and viral infection, ER homeostasis is disrupted, resulting in the accumulation of misfolded or unfolded proteins and the occurrence of ER stress[44-45]. The process of alveolar cell apoptosis has been identified as a contributing factor in the development of ALI in AKR mice[46]. Apoptosis and excessive apoptosis of pulmonary endothelial cells can compromise endothelial integrity and lead to pulmonary endothelial barrier dysfunction, which has been observed in patients with ARDS[47].

4.3 Pyroptosis Pyroptosis is a programmed cell necrosis mediated by the gastrin family (GSDM). This process is characterized by the swelling and rupture of cells, which results in the release of pro-inflammatory contents[48]. Pyroptosis encompasses two distinct inflammatory pathways: the classical pathway, which is dependent on caspase-1, and the non-classical pathway, which is dependent on caspase-4/5/11[49]. The activated caspase cleaves the substrate gastrin D (GSDMD) at the N-terminal domain of GSDMD, releasing mature IL-1β and IL-18 from the cell, thereby inducing cell lysis and amplifying the inflammatory response[50]. Bacteria, viruses, toxins, and drugs can cause pyroptosis, which helps to maintain the stability of the internal environment and combat external risk factor. There is growing evidence that pyroptosis occurs in different types of lung cells in the development of ALI[51], and pyroptosis of lung cells releases massive cytokines that destroy the alveolar epithelial structure and lung homeostasis, exacerbating ALI. Cheng Kwongtai *et al.* [52] found that endothelial cell pyroptosis is a key factor in the development of pulmonary edema and the subsequent onset of ALI and that therapeutic strategies to prevent endothelial cell pyroptosis may protect lung endothelial cell integrity and be beneficial for ALI/ARDS. LPS-induced ALI in mice was found to be ameliorated by the inhibition of macrophage pyroptosis[53-54]. Concurrently, it was found that in LPS-induced mouse ALIs, NETs formed during neutrophil NETosis may contribute to macrophage pyroptosis and exacerbate ALIs. Conversely, the degradation of NETs and the silencing of the AIM2 gene may prevent alveolar macrophage pyroptosis[55]. Current research shows that melatonin exerts a protective effect against ALI and pyroptosis induced by LPS. The mechanism of action is primarily through the activation of the Nrf2/HO-1 signaling axis, which results in the inhibition of the NLRP3-GSDMD pathway[56]. Therefore, the investigation of targets associated with lung cell pyroptosis may prove to be an efficacious approach to the alleviation of ALI.

4.4 Ferroptosis In addition, the ferroptosis is a novel form of programmed cell death that plays a significant role in the progression of several forms of ALI, including those induced by LPS[57], CCl_4[58], and intestinal ischemia/reperfusion[59]. Ferroptosis is a novel regulatory non-apoptotic form of cell death that is characterized by severe lipid peroxidation dependent on iron overload and ROS production. Ferroptosis is mainly caused by abnormal iron metabolism, lipid metabolism, and amino acid metabolism[60]. Excess iron-dependent ROS accumulation exceeds the cell's ability to maintain redox balance, leading to lipid peroxidation. Lipid peroxidation is a manifestation of cellular oxidative damage that increases cell permeability and ultimately leads to cell death[61]. GPX4, arachidonate lipoxygenases (ALOXs), fatty acids, XC- and iron are among the key regulators of ferroptosis. The current study shows that the pathway of iron overload disease mainly involves three aspects. (i) The GSH/Gpx4 pathway, XC inhibition system, sulfur transfer pathway, and p53 regulatory axis are involved. (ii) The autophagy proteins 5 and 7 (ATG5-ATG7) and nuclear receptor coactivator 4 (NCOA4) pathways and iron-responsive element binding protein 2 are involved in ferritin metabolism, and p62-Kelch-lekeeCH-associated protein 1 (Keap1)-Nrf2 regulatory pathway[62]. (iii) The lipid metabolism pathways, including p53, ALOX15, ACSL4, and LPCAT3, are also involved in the GTP cyclohydrolase 1-tetrahydrobiopterin 4 (GCH1-BH4), E-cadherin-nf2-Hippo-YAP and NADPH-inhibitory protein 1 (FSP1)-coenzyme Q10 (CoQ10) pathways[63]. The ferroptosis inhibitor Fer-1 effectively alleviates LPS-induced ALI and in vivo inflammatory response by regulating ferroptosis[64]. The results of Li Jin *et al.* [65] show that LPS can induce ferroptosis in lung tissue and in vitro and in vivo, exhibiting therapeutic effects on LPS-induced ALI through the use of ferroptosis inhibitors, thus providing new insights into the cell death pathway associated with ALI.

Therefore, the dysregulation of autophagy, apoptosis, pyroptosis, and ferroptosis is of critical importance in the development of ALI.

5 Endoplasmic reticulum stress

As the largest organelle in a cell, the endoplasmic reticulum (ER) is responsible for the biosynthesis of cellular lipids and proteins. Additionally, ER also provides an important modification and folding site for newly integrated membranes and secreted proteins. However, in the presence of specific pathological stimuli, the ER stress may be induced by the accumulation of misfolded proteins in ER[66]. When ER stress occurs, cells respond to changes in protein folding by activating the ER transmembrane sentinel proteins IRE1α, PERK, and ATF6, a process known as the unfolded protein response (UPR)[67-68]. The UPR can cause cell cycle arrest and down-regulate somatic gene expression and protein synthesis by increasing the expression of folded proteins and chaperone proteins, but if the expression of proteins and chaperone proteins is unable to prevent ER stress, the apoptotic cascade is initiated[69]. Studies have shown that during sepsis CLP, cold-induced RNA binding proteins (CIRPs) are released and interact with TLR4, leading to the activation of ER stress, which in turn causes inflammation and apoptosis, and ultimately ALI[70]. The activation of the ER-anchored protein HO-1 has been shown to alleviate ER stress by modulating the pERK/eIF2-α/ATF4/CHOP UPR signaling pathway, thereby exerting anti-apoptotic effects, reducing sepsis-induced ALI and improving lung function[71]. ER stress represents a significant pathogenic factor in the development of ALI, and the induction of ALI by a multitude of stimuli can be mitigated by the reduction of ER stress.

6 Coagulopathy

ALI is most commonly caused by pulmonary microvascular thrombosis. Following pathogen entry into the lung through the activation of the immune system and thromboinflammatory response, vascular endothelial damage leads to the loss of thromboprotective mechanisms, excessive thrombin production, and dysregulation of fibrinolysis and thrombosis, accompanied by damage to the alveolar-capillary barrier and abnormal activation of the coagulation system[72], which can trigger ALI. Coagulation coordinates inflammatory and tissue repair responses through the production of fibrin and the activation of the protease-activated receptor family, and the imbalance between coagulation and inflammation leads to the formation of hypercoagulable alveoli[73]. In ALI, coagulation abnormalities are important pathological changes, and an early inflammation-mediated hypercoagulable state may be a protective measure against the initiation of inflammation[74]. Conversely, the activation of the coagulation system and the imbalance of the fibrinolytic system have a pro-inflammatory effect. The coagulation factor and the fibrinolytic system produce various inflammatory factors, and the two cross-activate and interact to exacerbate the condition[75]. Autopsy studies have shown that both macrovascular and microvascular thromboses are prevalent among ARDS patients (up to 95% of patients)[76]. In addition, thrombosis is associated with neutrophils, and due to increased expression of ICAM-1 in endothelial cells, neutrophils adhere more effectively to activated platelets, and inhibition of platelet-neutrophil aggregation has been shown to improve gas exchange, reduce neutrophil recruitment and neutrophil permeability in the sepsis-induced ALI model[77]. Improving coagulopathy has become a treatment for ALI because coagulation activation is both a consequence and a cause of persistent lung injury.

7 Aquaporin

ALI is a serious pulmonary disease characterized by hypoxemia and bilateral pulmonary infiltrates. For patients with ALI, the effective removal of edema fluid from the alveoli is of critical importance in order to ensure the effective gas exchange. Alveolar fluid clearance (AFC) is an important element in the treatment of ALI, with aquaporins(AQPs) serving a pivotal role in AFC[78]. Often referred to as "water channels", AQPs are a family of small, intact membrane proteins that facilitate the transport of water across cell membranes. These proteins are expressed in a wide range of organs, including the lungs, kidneys, central nervous system, heart, skin, and eyes[79]. AQPs are expressed in the epithelial and endothelial cells of various organs and play a normal physiological role in promoting fluid transport; in the respiratory system, the specific distribution of AQPs in tissues and cell types and their developmental regulation suggest that AQPs play a similar role in fluid transport and normal lung physiology[80]. Of the 13 AQPs in humans, lung tissue and airways are the principal sites of expression for AQPs 1, 3, 4, and 5[81]. The early impairment of the alveolar epithelium and capillary endothelial cells results in the dysfunction of alveolar sodium and water transport, as well as fluid retention in the alveolar space and aggregation of inflammatory cells[82]. Lung injury is associated with increased vascular permeability, elevated vasoactive intestinal peptide (VIP) levels in lung tissue, and cyclic adenosine monophosphate (cAMP)/PKA downregulation of AQPs expression, which in turn affects the normal water metabolism of lung tissue cells[80]. This leads to pulmonary edema, which is characterized by water accumulation in the lungs. This phenomenon is observed in various ALI models. The ALI model suggests that AQP1 and AQP5 play an important role in the development of lung injury or edema[83].

8 Conclusions

ALI/ARDS is a refractory inflammatory disease in the ICU with a high mortality rate. Therefore, it is urgent to identify effective treatment methods for ALI. The most crucial step in this process is to understand the pathogenesis of ALI/ARDS. However, the pathogenesis of ALI/ARDS remains unknown. ALI is a disease with a complex pathogenesis and a variety of factors may predispose to ALI. This article presents a summary of the pathogenesis of ALI.

It is concluded that the activation of NLRP3 inflammasomes, JAK2/STAT3, PI3K/Akt/MAPK, TLR4/NF-κB and other related inflammatory signaling pathways, which result in the dysregulation of inflammatory cytokines due to excessive inflammation, is the primary pathogenesis of ALI. In addition, Nrf2/HO-1 down-regulates excessive oxidative stress, GSH, and iron ion accumulation. Conversely, Nrf2/HO-1 down-regulation leads to excessive release of ROS, which in turn causes iron death. Furthermore, the activation of Bax/Bcl-2 pathway results in apoptosis, and the activation of the RIPK1/RIPK3/MLKL pathway results in the programmed necrosis and autophagy of cells, accompanied by an increase in ER stress, the release of factor VIII and von Willebrand factor (VWF) by endothelial cells, and a decline in the function of AQP1/5, which collectively contribute to the development of ALI. A number of pathogenic mechanisms interact in order to exacerbate ALI. Complement activation has been demonstrated to promote cytokine storms and coagulation dysfunction. Furthermore, the complement system has been shown to affect the phagocytosis of neutrophils and monocytes. Additionally, ER stress has been linked to apoptosis, autophagy, and inflammatory response. The interaction between these mechanisms may be responsible for the high incidence and mortality of ALI.

At present, studies have proved that ALI/ARDS has multiple potential pathogenesis pathways. However, it is currently believed that the endpoint of the pathogenesis of ALI/ARDS points to inflammation, and the exploration of the connection between other potential pathogenesis pathways and inflammation is still in its infancy. In addition, the pathogenesis and drugs developed for this purpose are still largely in the preclinical research phase, with only a small number of drugs having entered clinical trials. Future endeavors are guided by the following principles. (i) An in-depth study of the connections between pathogenesis and the identification of potential bridges between them is essential to elucidate the pathogenesis of ALI/ARDS. (ii) The identification of biomarkers in each pathogenesis is also crucial. (iii) Finally, clinical trials to test new drugs are necessary to advance the field. This will facilitate the development of more effective strategies for the treatment of ALI/ARDS, thereby reducing mortality and improving the quality of life of those affected.

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