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Study on the Regulatory Mechanism and Targeted Therapy of Autophagy in Acute Respiratory Distress Syndrome

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Abstract: Acute Respiratory Distress Syndrome (ARDS) causes significant mortality worldwide, yet lacks specific pharmacological interventions. Autophagy, a critical cellular response to ARDS triggers like infection and hypoxia, regulates alveolar repair and immune modulation. Although macroautophagy is extensively characterized in ARDS, microautophagy and chaperone-mediated autophagy (CMA) remain poorly understood. This paper comprehensively reviews the molecular mechanisms of all three autophagy subtypes in ARDS, highlighting their potential as novel diagnostic markers and therapeutic targets.

Keywords: Macroautophagy; Microautophagy; Chaperone-mediated autophagy; Acute Respiratory Distress Syndrome

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1. Pathological Characteristics and Inflammatory Mechanisms of ARDS

1.1. Clinical Definition and Epidemiological Features of ARDS

Acute Respiratory Distress Syndrome (ARDS) is an acute, diffuse lung injury triggered by diverse etiologies[1], diagnosed based on the 2012 Berlin Definition[2]. Epidemiologically, ARDS is a prevalent critical condition in intensive care units (ICUs) globally, affecting approximately 10.4% of mechanically ventilated patients. Mortality remains high and correlates directly with severity: 28-day mortality rates for mild, moderate, and severe ARDS are 34.9%, 40.3%, and 46.1%, respectively[3]. The COVID-19 pandemic precipitated a surge in SARS-CoV-2-associated ARDS, significantly elevating overall mortality rates regardless of medical resource availability. Primary high-risk populations include patients with sepsis, severe pneumonia, major trauma, and pancreatitis [4].

1.2. Core Pathophysiological Changes of ARDS

ARDS pathophysiology centers on alveolar-capillary barrier failure, causing proteinaceous edema, surfactant dysfunction, and heterogeneous alveolar collapse ("baby lung")[5]. This leads to severe ventilation/perfusion mismatch and

intrapulmonary shunting, resulting in refractory hypoxemia unresponsive to supplemental oxygen—the hallmark clinical challenge of the syndrome [6].

1.3. Molecular and Cellular Mechanisms of Uncontrolled Inflammatory Response in ARDS

Pulmonary injury during ARDS is essentially an excessive and uncontrolled innate immune inflammatory storm, driven by a vicious cycle of multi-level, positive feedback molecular and cellular mechanisms. After pathogen-associated molecular patterns or damage-associated molecular patterns are recognized by alveolar macrophages and epithelial cells, key signaling pathways such as NF-κB are activated, triggering massive release of early pro-inflammatory factors including TNF-α, IL-1β, and IL-6, forming a "cytokine storm". This further recruits and activates a large number of neutrophils to infiltrate lung tissue, significantly amplifying the inflammatory cascade[7].

In this process, multiple inflammasomes including NLRP3, NLRC4, and AIM2 can be activated by different danger signals, jointly promoting the escalation of inflammation to an uncontrollable state. Inflammasome assembly triggered by danger signals such as reactive oxygen species, mitochondrial DNA, bacterial flagellin, or cytoplasmic double-stranded DNA activates caspase-1, which not only cleaves pro-IL-1β and pro-IL-18 into mature active forms but also induces pyroptosis, further exacerbating tissue damage and inflammatory spread[8].

As the executors of injury, infiltrating neutrophils directly destroy lung parenchymal structures by releasing elastase, matrix metalloproteinases, and myeloperoxidase, and cause endothelial/epithelial barrier damage by forming neutrophil extracellular traps (NETs), while providing scaffolds for microthrombi[9]. Meanwhile, activated inflammatory cells and dysfunctional mitochondria continuously produce excessive reactive oxygen species, inducing extensive oxidative stress. This not only directly damages biological macromolecules but also acts as signaling molecules to continuously activate pathways such as inflammasomes, forming a self-reinforcing oxidative cycle.

Notably, inflammation and the coagulation system are deeply coupled: inflammatory factors and damaged endothelium induce high expression of tissue factor, initiating the coagulation cascade and leading to extensive microthrombus formation in pulmonary microvessels; the fibrinolytic system is inhibited due to significantly elevated PAI-1 levels, hindering thrombus clearance[10]. This "immunothrombosis" not only aggravates hypoxia and microcirculatory disorders but also releases more inflammatory mediators through platelets, forming a fatal "inflammation-coagulation vicious cycle" with inflammatory responses, ultimately driving ARDS progression to irreversible multiple organ dysfunction[11].

2. Mechanisms of Autophagy

2.1. Macroautophagy

Macroautophagy is the most classical form of autophagy, characterized by the formation of double-membraned autophagosomes that encapsulate intracellular substances to be degraded and fuse with lysosomes for substrate degradation and nutrient recycling. It is a highly conserved intracellular degradation pathway in eukaryotes, requiring the coordinated action of more than 30 autophagy-related proteins (ATGs)[12].

The complete process is divided into four stages: autophagy initiation, autophagosome formation and maturation, autophagosome-lysosome fusion, and substrate degradation and recycling, regulated by a precise molecular signaling network. Autophagy initiation is centered on mTORC1 as the core switch: under nutrient-rich conditions, mTORC1 phosphorylates ULK1 to inhibit the activation of the autophagy initiation complex; under stress conditions such as nutrient deprivation, AMPK is activated, relieving the inhibition and initiating autophagy by directly phosphorylating ULK1 or indirectly inhibiting mTORC1. Endoplasmic reticulum calcium transients also assist in the formation of autophagosome initiation sites[13].

Autophagosome formation relies on two ubiquitin-like conjugation systems: the ATG12-ATG5-ATG16L1 complex mediates autophagosomal membrane elongation, and WIPI2 recruits it to nascent sites; the LC3 precursor is processed and

lipidated with PE to form LC3-II, which anchors to the membrane and recognizes substrates[14]. The endoplasmic reticulum is an important origin of autophagosomal membranes, and ATG2 proteins transfer phospholipids to promote membrane elongation .

Autophagosome-lysosome fusion is mediated by SNARE family proteins such as Syntaxin17, achieving membrane docking to form autolysosomes with the support of the VPS34-Beclin1 complex[15]. Subsequently, lysosomal acid hydrolases degrade substrates into small molecules for cellular metabolic recycling, maintaining homeostasis under stress. Macroautophagy has both non-selective and selective forms, regulated by pathways such as mTOR/AMPK and dependent on the coordination of numerous ATGs. Its dysfunction is closely related to cancer, neurodegenerative diseases, etc., providing important targets for therapeutic research of related diseases.

2.2. Microautophagy

Microautophagy is a form of autophagy in which lysosomal or late endosomal membranes directly invaginate or protrude to uptake and degrade cytoplasmic components, independent of the formation of independent double-membraned autophagosomes[16]. The invagination of lysosomal or endosomal membranes requires the participation of the Endosomal Sorting Complex Required for Transport (ESCRT).

The microautophagy process can be divided into two orderly stages: substrate recognition, and membrane invagination and degradation. In the substrate recognition stage, ubiquitination is the main molecular tag. Damaged proteins, abnormal organelles, or other substances to be degraded are often labeled with ubiquitin and thus recognized by ESCRT-0 components and recruited to endosomal or lysosomal membranes. For example, ubiquitinated pro-IL-1β can be selectively delivered to lysosomes for degradation through this pathway, achieving post-transcriptional inhibition of inflammatory responses.

In addition, in specific types of microautophagy, Atg8 family proteins can anchor to lysosomal membranes through atypical lipidation to assist substrate recruitment and membrane remodeling[17]. For mitochondria-associated microautophagy, recent studies have found that ESCRT-III can selectively remove mitochondrial outer membrane fragments, and the PINK1-PRKN pathway, although mainly involved in macroautophagic mitophagy, may indirectly affect substrate selection of microautophagy under certain stress conditions.

In the membrane invagination and degradation stage, the ESCRT complex exerts a core executive function: ESCRT-I and ESCRT-II initiate membrane deformation, ESCRT-III (e.g., CHMP4B) assembles into helical polymers at the membrane neck, driving membrane inward invagination and finally completing membrane scission mediated by VPS4 ATPase[18]. This process is not only used to degrade cytoplasmic components but also plays a key role in lysosomal membrane damage repair. When lysosomal membranes rupture, ESCRT-III is rapidly recruited to damaged sites to remove impaired regions and restore membrane integrity through a microautophagy-like mechanism.

Meanwhile, V-ATPase maintains the acidic environment in the lysosomal lumen to ensure hydrolase activity, and its dysfunction significantly weakens microautophagy efficiency; transcription factor TFEB provides a structural basis for sustained microautophagy by promoting lysosomal biogenesis[19]. In addition, serine/threonine kinase STK38 has been found to cooperate with ESCRT to participate in reparative microautophagy of damaged lysosomes, further ensuring the homeostatic operation of this pathway[20].

2.3. Chaperone-Mediated Autophagy (CMA)

Chaperone-Mediated Autophagy (CMA) is a selective degradation mechanism characterized by the exclusive degradation of soluble cytoplasmic proteins containing specific recognition sequences, without involving membrane remodeling or vesicle formation. Unlike macroautophagy and microautophagy, CMA directly transports substrate proteins across membranes into lysosomal lumens for degradation through molecular chaperones[21].

The degradation process of CMA has strict molecular specificity and stepwise regulation, relying on the coordinated action of molecular chaperones and lysosomal membrane receptors. First, in the substrate recognition stage, the

cytoplasmic core molecular chaperone heat shock cognate protein 70 (HSC70) specifically recognizes and binds to a conserved pentapeptide motif on substrate proteins, namely KFERQ or its similar sequences[22]. Approximately 30% of cytoplasmic proteins contain such motifs, including glycolytic enzymes, transcription factors, and oxidatively damaged or misfolded proteins.

Subsequently, the HSC70-substrate complex is targeted to the lysosomal membrane and binds to the specific receptor lysosome-associated membrane protein type 2A (LAMP2A). LAMP2A is the rate-limiting step and marker protein of CMA, and its expression level and oligomerization state directly regulate CMA pathway activity[23]. Finally, in the transmembrane transport and degradation stage, substrate-bound LAMP2A assembles into oligomeric channels on the membrane, and with the assistance of another molecular chaperone in the lysosomal lumen (lys-Hsc70), transports unfolded substrate proteins unidirectionally into the lysosomal lumen for complete degradation by hydrolases.

CMA activity is precisely regulated under physiological and pathological conditions. Under conditions such as nutrient deprivation, oxidative stress, and proteotoxic stress, CMA activity can be upregulated to play a key role in maintaining cellular protein homeostasis and metabolic adaptation by removing damaged proteins and providing amino acid resources[24].

3. Mechanisms and Current Therapeutic Status of Autophagy in ARDS

3.1. Macroautophagy

Macroautophagy is the most extensively studied form of autophagy, exerting a typical “double-edged sword” effect in ARDS by regulating cellular barrier function, inflammatory responses, and organelle homeostasis. Its direction of action is highly correlated with pathogenic factors, disease stages, and cell types[25].

In the early or mild injury stage of ARDS, moderately activated macroautophagy acts as a key adaptive defense mechanism for cells to cope with pathological stress, functioning in different cells to systematically alleviate lung tissue damage and maintain functional homeostasis. In parenchymal cells constituting the alveolar-capillary barrier—including alveolar epithelial cells and pulmonary vascular endothelial cells—the core protective effect of macroautophagy is reflected in timely removal of endogenous damaged substances such as dysfunctional mitochondria and misfolded proteins through selective autophagy pathways, thereby inhibiting excessive reactive oxygen species production, alleviating endoplasmic reticulum stress, and reducing apoptosis[26].

In addition, macroautophagy can promote the proliferation and differentiation of type II alveolar epithelial cells and surfactant secretion, and stabilize tight junction proteins and cytoskeletons of endothelial cells, jointly maintaining the barrier integrity of alveolar epithelium and vascular endothelium, directly reducing pulmonary edema and tissue damage[27]. Meanwhile, at the immune regulatory level, especially in alveolar macrophages, macroautophagy effectively prevents the release of damage-associated molecular patterns (DAMPs) such as mitochondrial DNA through the same precise mitophagy mechanism, thereby inhibiting excessive inflammasome activation, reducing the secretion of pro-inflammatory factors such as IL-1β and IL-18[28], and promoting the polarization of alveolar macrophages to the anti-inflammatory M2 phenotype, significantly blocking inflammatory cascades in sepsis models[29].

Studies have also shown that exosome-delivered miR-223-3p can enhance macroautophagy in alveolar macrophages by inhibiting STK39 expression, thereby alleviating lung injury[30]. Furthermore, in pathogen infection-related ARDS, macroautophagy can directly degrade intracellular viral particles through “xenophagy” to limit their replication and spread[31].

However, in severe sepsis and persistent hyperinflammatory states, excessive activation of macroautophagy may lead to autophagic cell death or cross-activation with apoptosis and pyroptosis pathways, accelerating the loss of alveolar epithelial and endothelial cells. Under specific pathological backgrounds, sustained activation of macroautophagy may shift from protection to injury[32]. Therefore, intervention strategies targeting macroautophagy need to emphasize “temporal precision”—induction in the early stage to enhance defense, and inhibition in the late stage to prevent excessive

degradation.

3.2. Microautophagy

Compared with macroautophagy, research on microautophagy in ARDS is almost in a blank state, but its unique direct lysosomal degradation mechanism makes it a highly potential emerging regulatory node. Microautophagy does not rely on autophagosome formation but directly uptakes cytoplasmic components through lysosomal or endosomal membrane invagination, a process mainly mediated by the ESCRT complex.

Recent studies have found that ESCRT can specifically recognize ubiquitinated pro-IL-1β and deliver it to lysosomes for degradation through the microautophagy pathway, thereby inhibiting IL-1β maturation at the source[33]. Given that IL-1β is a core mediator driving the "cytokine storm" in ARDS, microautophagy may play a key negative regulatory role in limiting inflammasome downstream effects, which is highly consistent with the logic of inhibiting "cytokine storm" in ARDS.

In addition, lysosomes can directly phagocytose damaged mitochondrial outer membrane fragments through microautophagy[34]. In LPS-induced alveolar epithelial cell injury models, deletion of the ESCRT-III component CHMP2A leads to mitochondrial ROS accumulation and elevated inflammatory factor levels, suggesting that impaired microautophagy may trigger severe inflammatory responses.

The role of microautophagy in maintaining organelle homeostasis has also been verified. Reticulophagy is a known means of selectively removing damaged endoplasmic reticulum, and the function of its receptor proteins is crucial for alleviating endoplasmic reticulum stress. Studies have revealed that lysosomes can directly phagocytose mitochondrial outer membrane fragments through ESCRT-dependent microautophagy, providing cutting-edge evidence for the complementary role of microautophagy in mitochondrial quality control[35].

3.3. Chaperone-Mediated Autophagy

Chaperone-mediated autophagy is a highly selective degradation pathway that relies on HSC70 to recognize substrate proteins containing KFERQ motifs and mediates their translocation across the lysosomal membrane through LAMP2A. Currently, CMA function declines with age and is closely associated with various neurodegenerative diseases; however, its role in ARDS has not been reported. Nevertheless, based on the proven core biological functions of CMA, it is reasonable to speculate its potential protective role in the pathological process of ARDS.

First, in terms of inflammatory regulation, CMA can inhibit LPS-induced cellular inflammatory responses in a LAMP2A-dependent manner, significantly downregulate iNOS/COX-2 expression, reduce NO release, and inhibit the production of pro-inflammatory factors such as IL-6 and IL-1β, thereby exerting anti-inflammatory effects[36].

Second, in response to oxidative stress, CMA is recognized as an important mechanism for clearing oxidatively damaged or misfolded proteins in the cytoplasm. Oxidative stress can activate transcription factors NRF2 and NFAT1, thereby upregulating LAMP2A expression and enhancing CMA activity[37]; CMA specifically degrades damaged proteins by recognizing exposed KFERQ-like sequences, maintaining cellular protein homeostasis. This mechanism is highly consistent with the pathological features of severe oxidative damage and abnormal protein accumulation leading to cellular dysfunction in ARDS lung tissue.

In addition, CMA indirectly regulates mitochondrial homeostasis. Although CMA cannot degrade proteins localized in mitochondria, it can inhibit excessive mitochondrial fragmentation by degrading the key mitochondrial fission protein MARCHF5, maintain mitochondrial network stability and reduce reactive oxygen species production, and also degrade nuclear-encoded abnormal mitochondrial proteins to avoid mitochondrial dysfunction caused by their accumulation. Given that mitochondrial dysfunction is an important pathological link in ARDS, the protective potential of CMA in this process deserves in-depth exploration.

In summary, CMA plays important roles in inflammatory regulation, oxidative stress response, and mitochondrial homeostasis maintenance. Although there are no studies on CMA in ARDS, CMA has clear mechanistic correlations with

key pathological links of ARDS such as inflammatory storm, oxidative damage, and mitochondrial dysfunction. The specific regulatory relationship between them still needs targeted research for further verification.

4. Conclusion

This review highlights the critical yet distinct roles of the three autophagy pathways in ARDS: the dual-edged macroautophagy, the surfactant-regulating microautophagy, and the repair-focused chaperone-mediated autophagy. Although their individual contributions are emerging, their dynamic interactions across disease stages remain unclear. Leveraging advanced imaging and genomic tools to decode these mechanisms holds promise for developing precise, autophagy-based therapeutics to combat ARDS.

Disclosure statement

The author declares no conflict of interest.

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