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Research Progress on Dexmedetomidine Regulating Autophagy in the Treatment of Acute Lung Injury

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Abstract: Dexmedetomidine, extensively utilized as an intravenous anesthetic in anesthesia, intensive care units, and other related medical departments, exhibits significant anti-inflammatory effects while inducing sedation. Numerous studies have demonstrated its capability to regulate autophagy, thereby exerting potent anti-inflammatory effects and offering therapeutic benefits in the treatment of acute lung injury. This article comprehensively reviews the mechanisms underlying autophagy, the role of dexmedetomidine in autophagy regulation, and the protective effects it conders in the context of acute lung injury. By doing so, it contributes positively to the arsenal of strategies aimed at both preventing and treating acute lung injury.

Keywords: Dexmedetomidine; Acute lung injury; Autophagy

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1. Introduction

Acute lung injury (ALI) manifests as damage to alveolar epithelial cells and capillary endothelial cells, a consequence of severe pulmonary/extrapulmonary infections, shock, trauma, and various diseases. This damage leads to diffuse pulmonary interstitial and alveolar edema, potentially culminating in respiratory insufficiency or failure. In more severe cases, it can progress to acute respiratory distress syndrome (ARDS), marked by tachypnea, cyanosis, oxygen transport dysfunction, and diminished lung compliance [1].

Current treatment modalities for ALI/ARDS encompass protective mechanical ventilation, drug therapy, Chinese herbal medicine, extracorporeal membrane oxygenation, and fluid management. Despite progress, a specific treatment approach for ALI/ARDS remains elusive. Even with available drugs, the associated mortality rate remains alarmingly high [2].

Given this scenario, the exploration of effective treatments for ALI assumes paramount importance. This

article aims to contribute to this imperative task by examining the intricate landscape of ALI, shedding light on existing treatment methods, and emphasizing the pressing need for innovative and targeted interventions.

2. Autophagy and the role of autophagy in acute lung injury

2.1. The definition and process of autophagy

The term "autophagy," derived from Greek, translates to "eating oneself," encapsulating the concept of self-degradation. Autophagy represents a highly conserved cellular process, crucial for cell survival and the maintenance of the internal environment. This process involves the degradation of aging organelles, denatured proteins, and various macromolecular substances, coupled with the recycling of resulting decomposition products [3]. Autophagy, therefore, stands as a fundamental mechanism contributing to cellular health and the preservation of the internal milieu.

2.2. Signal transduction pathways related to autophagy

The mammalian target of rapamycin (mTOR) kinase stands out as a crucial regulatory molecule for initiating autophagy. Pathways activating mTOR, such as the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases 1 and 2 (ERK1/2) and phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) pathways, act as inhibitors of autophagy. Conversely, negative regulation of mTOR, facilitated by pathways such as AMP-activated protein kinase (AMPK) and tumor protein p53, promotes autophagy. For instance, growth factors can activate the PI3K/Akt pathway, subsequently activating mTOR and inhibiting autophagy.

The core protein unc-51-like kinase (ULK), endowed with serine/threonine kinase activity, forms the ULK1 serine/threonine kinase complex [comprising ULK1, scaffolding subunit FAK family kinase-interacting protein of 200 kD (FIP200), bridging subunit Atg13, and Atg101]. ULK1 catalyzes the phosphorylation of various downstream factors, playing a pivotal role in autophagy initiation. AMPK and mTOR catalyze ULK1 phosphorylation; when the body faces energy insufficiency, activated AMPK promotes ULK1 phosphorylation, thereby stimulating autophagy. Activated ULK1, in turn, recruits the PI3K class III complex (comprising Beclin-1, Atg14, phosphatidylinositol 3-kinase Vps34, and serine/threonine-protein kinase Vps15), perpetuating autophagy induction [4].

Autophagosome formation, a critical autophagy step, involves distinct phases such as formation, nucleation, elongation, and isolation membrane closure. Autophagy-related genes (Atg) are evolutionarily conserved and are indispensable for autophagosome formation, contributing significantly to autophagy-related signal transduction pathways. Atg9A-containing vesicles supply the membrane structure for autophagosomes, and the extension and completion of the autophagosome membrane involve two ubiquitin-like protein binding systems: firstly, Atg12 binding to Atg5 and Atg16L1, promoting LC3 lipidation by phosphatidylethanolamine (PE); secondly, Atg4B-mediated microtubule-associated protein 1A/1B-light chain 3 (LC3) processing, forming LC3-I, which binds with PE on the membrane to generate LC3-II. This structure adheres to the autophagosome membrane and collaborates with autophagic vesicles, crucially participating in autophagy initiation [5].

PTEN-induced kinase 1 (PINK1), a serine/threonine kinase, with its kinase activity and structural integrity prerequisites, triggers the translocation of E3 ubiquitin ligase Parkin to damaged mitochondria, inducing mitophagy. In response to mitochondrial damage, PINK1 accumulates in the outer membrane, activating and recruiting Parkin. This culminates in Parkin ubiquitin modification of outer membrane proteins, subsequently binding to microtubule-related proteins. This binding process packages affected proteins into autophagosomes, facilitating their combination with lysosomes for the degradation and clearance of damaged mitochondria.

2.3. The role of autophagy in ALI: influencing factors and mechanisms

Autophagy's involvement in ALI is multifaceted, triggered by diverse factors encompassing infectious elements like bacteria and viruses, along with non-infectious contributors such as toxic gas inhalation, extensive blood transfusions, and acute pancreatitis. Autophagy, as a contributing mechanism to ALI, exhibits a dual nature. On one hand, it serves a protective function by clearing harmful inflammatory factors from the body, consequently mitigating lung damage. Conversely, autophagy can induce apoptosis, thereby intensifying lung injury. Insufficient, diminished, or excessive autophagy all contribute to the exacerbation of lung tissue damage [6].

In a *Pseudomonas aeruginosa* infection model, CoB1, a novel cochlioquinone B derivative, disrupts the Akt/mTOR pathway by facilitating ubiquitination-mediated degradation of serine/threonine-protein kinase PAK1. This process activates autophagy following CoB1 treatment, resulting in increased mouse survival rates and reduced inflammatory factors. This evidence establishes that autophagy induction holds the potential to diminish lung injury. In a lipopolysaccharide (LPS)-induced acute lung injury model, LPS activation of mTOR reduces autophagy in mouse airway epithelial cells. Contrarily, LC3B, an autophagy protein in human bronchial epithelial cells, experiences reduced autophagy, aggravating the inflammatory response in lung tissue. The inhibition of the mTOR pathway significantly diminishes endotoxin-induced ALI, providing substantial proof that augmenting autophagy is advantageous in reducing ALI.

3. Mechanism of dexmedetomidine in regulating autophagy and its protective effect on ACI

Dexmedetomidine (DEX), a highly selective alpha2 adrenergic receptor agonist, holds broad applications in clinical anesthesia, intensive care units, and other medical domains. Autophagy, recognized as an adaptive catabolic process, has garnered attention due to mounting evidence illustrating DEX's significant protective effects on various organs. Autophagy plays a pivotal role in mitigating organ damage under DEX treatment by influencing diverse signaling pathways and their downstream molecules, such as toll-like receptor 4 (TLR-4), myeloid differentiation primary response 88 (Myd88), nuclear factor-κβ (NF-κβ), among others. This inhibition results in the suppression of pro-inflammatory factor release, manifesting in anti-inflammatory effects and effective ALI treatment.

In a rat model of lung injury induced by hemorrhagic shock, DEX treatment markedly ameliorated lung tissue congestion, edema, inflammation, and bleeding. Concurrently, the expression of autophagy proteins, including LC3, Beline-1, and Atg12-Atg5 conjugates, exhibited significant increases, while the expression level of multifunctional protein p62 significantly decreased. When the autophagy inhibitor chloroquine (CQ) was combined with DEX, the protective effect on lung histopathology weakened. Beclin-1 expression was affected and decreased, Atg12-Atg5 conjugate expression was lower compared to the DEX group, and p62 expression was higher [7]. CQ was also found to block autophagosomes and lysates in the final stage of autophagy. This underscores the positive correlation between DEX's protective effect on the lungs and autophagy.

In acute myocardial ischemia/reperfusion (MIR) injury, DEX demonstrated its efficacy by upregulating PINK1 transcription to enhance mitophagy. Through the alpha2 adrenergic receptor, it inhibited the PI3K/Akt/mTOR pathway, thereby increasing the transcription and translation of LC3 and Beclin-1. This led to the restoration of autophagy, reduction in oxidative stress, and mitigation of apoptosis in LPS-induced acute kidney injury. In LPS-induced ALI, DEX exhibited protective effects by potentially mediating TLR-4/NF-κβ and PI3K/Akt/mTOR pathways through high mobility group box-1 protein (HMGB1), a potential upstream regulator of TLR-4. Additionally, in subarachnoid hemorrhage (SAH)-induced extracerebral organ dysfunction, DEX treatment reduced autophagic flux and TLR-dependent inflammatory pathways, alleviating subarachnoid ALI

caused by intracavitary hemorrhage. In a ventilator-associated lung injury (VILI) model, DEX pretreatment significantly reduced Bcl-2 homologous antagonist/killer (Bak)/B-cell lymphoma 2 (Bcl-2) ratio, caspase-3 expression levels, epithelial cell death, and inflammatory factor release. This protective effect was associated with the activation of the ERK1/2 signaling pathway, as evidenced by increased phosphorylated ERK1/2 expression. The study suggested that DEX protects alveolar epithelial cells by activating the ERK1/2 signaling pathway, thus mitigating ventilator-induced lung injury [8].

4. Summary

In brief, dexmedetomidine demonstrates the ability to alleviate acute lung injury stemming from diverse factors through various mechanisms. While numerous current studies underscore dexmedetomidine's efficacy in treating acute lung injury by modulating autophagy, it is noteworthy that the majority of these findings are derived from animal experiments and cellular studies. The specific mechanism remains largely unexplored. Future research endeavors will delve into the intricate details of how dexmedetomidine precisely influences autophagy and its integral role in mitigating organ damage.

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Disclosure statement

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