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REVIEW

Acute Lung Injury and the NLRP3 Inflammasome

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Abstract: Acute lung injury (ALI) manifests through harm to the capillary endothelium and alveolar epithelial cells, arising from a multitude of factors, leading to scattered interstitial alterations, pulmonary edema, and subsequent acute hypoxic respiratory insufficiency. Acute lung injury (ALI), along with its more serious counterpart, acute respiratory distress syndrome (ARDS), carry a fatality rate that hovers around 30–40%. Its principal pathological characteristic lies in the unchecked inflammatory reaction. Currently, the main strategies for treating ALI are alleviation of inflammation and prevention of respiratory failure. Concerning the etiology of ALI, NLRP3 Inflammasome is essential to the body's innate immune response. The composition of this inflammasome complex includes NLRP3, the pyroptosis mediator ASC, and pro-caspase-1. Recent research has reported that the inflammatory response centered on NLRP3 inflammasomes plays a key part in inflammation in ALI, and may hence be a prospective candidate for therapeutic intervention. In the review, we present an overview of the ailment characteristics of acute lung injury along with the constitution and operation of the NLRP3 inflammasome within this framework. We also explore therapeutic strategies targeting the NLRP3 inflammasome to combat acute lung injury.

Keywords: acute lung injury, NLRP3 inflammasome, caspase-1, IL-1β, IL-18

Introduction

The pandemic-causing influenza and emerging viruses have brought about sporadic spikes in global acute lung injury (ALI). ALI manifests through injury to the cells lining the alveoli and those composing the capillary walls, which leads to interstitial and alveolar edema within the lungs, thus leading to a severe shortage of oxygen causing respiratory distress.[1,2] ALI presents with reduced pulmonary capacity, diminished elasticity within the lungs, and a profound disruption of the ventilation-perfusion balance.[3] When left untreated, acute lung injury (ALI) can develop into acute respiratory distress syndrome (ARDS).[4] Despite advancements in grasping the fundamental processes that lead to acute lung injury (ALI), an effective targeted treatment for the condition remains elusive. While ALI morbidity and mortality have declined, the death rate associated with ALI and ARDS continues to hover around a staggering 30 to 40%. It is typified by an unchecked inflammatory reaction. Currently, the main strategies for treating ALI are reduction of inflammation and prevention of respiratory failure. Consequently, gaining a deeper comprehension of the inflammatory origins of ALI and stalling its advancement is crucial.

The NLRP3 inflammasome, recognized as the extensively studied NLR receptor family member, is widely present across various immune cells and holds a crucial part in the body's immune system, safeguarding the body against the infiltration of infectious agents. This intricate entity comprises a detector (NLRP3), a connector (equipped with the c-terminal cysteine protease enlistment domain, ASC), and an executor (caspase-1). It is a vital element of the innate immune system, enabling the development of active caspase-1 as well as the following development and production of inflammatory cytokines IL-1β and IL-18.[5] Important functions in the inflammatory response are played by IL-1β and IL-18.

Activating the NLRP3 inflammasome is a critical stage in the development of ALI. In ALI/ARDS patients, elevated IL-1β and IL-18 levels correlate with unfavorable outcomes. One study found that levels of IL-1β were markedly increased in the BALF of mice with ALI model produced by LPS, and the expression of NLRP3 protein was noticeably higher in lung tissue. The NLRP3 inflammasome acts as an important catalyst and accelerator of ALI. By coordinating

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the discharge of pro-inflammatory cytokines.[6] Consequently, hindering the stimulation of the NLRP3 inflammasome has the potential to be a viable method in managing ALI.

In this review, we offer a succinct overview of ALI, followed by an in-depth look at the make-up and triggering of the NLRP3 inflammasome. We investigate the link between ALI and the NLRP3 inflammasome, as well as potential therapy options for ALI.

Acute Lung Injury

Concept

Since the initial conceptualization of acute respiratory distress syndrome (ARDS) back in 1967, there has been remarkable advancement in unraveling the mechanisms underlying its onset and progression, as well as the physiological changes associated with acute lung injury (ALI).[7] ALI presents as a grave medical emergency, carrying a death rate of approximately 30 to 40%. Its characteristics include the aggregation of inflammatory cells in pulmonary tissue, loss of alveolar-capillary membrane integrity, interstitial edema, abnormal gas exchange, and alveolar septal damage. Treatment approaches for ALI remain very limited in their efficacy.[8]

Diagnostic Criteria

The diagnostic criteria for ALI/ARDS have undergone several changes over the years. In 1988, the system for assessing the degree and severity of lung injury was proposed by Murray et al.[9] In 1994, the American-European Consensus Conference (AECC) laid down the definition for ALI/ARDS and set forth the subsequent diagnostic criteria: chest x-rays showing acute bilateral diffuse pulmonary infiltrates; a PaO2/FiO2 ratio ≤300 mmHg for ALI and ≤200 mmHg for ARDS; and either PAWP ≤18 mmHg or absence of indications of left atrial hypertension. This set of criteria first introduced the concept of ALI, with ARDS considered a more severe form of ALI warranting significant attention in the early days of ALI.[10] However, the AECC criteria faced many clinical issues. In 2012, a collaborative committee comprising the European Society of Intensive Care Medicine, the American Thoracic Society, and the American Society of Critical Care Medicine unveiled the Berlin Criteria for ARDS. ARDS is categorized into different levels based on the degree of hypoxemia- mild (PaO2/FiO2 is between 200mmHg to 300mmHg), moderate (PaO2/FiO2 is between 100mmHg to 200mmHg), and severe (PaO2/FiO2 is less than or equal to 100mmHg).[11] Compared to earlier attempts, the Berlin Criteria provide a better prediction of mortality and do not require measuring pulmonary capillary wedge pressure.

Etiological Factors

The etiology of ALI is complex, with pneumonia being a leading factor causing ARDS and ALI.[12] Sepsis and gastric content aspiration are common reasons for pulmonary impairment.[13,14] There are also some less common factors, such as massive transfusion, blast waves, smoke inhalation, and toxic gas inhalation.[15–18] If two or more of these risk factors are present at the same time, the probability of developing ALI or ARDS becomes higher. For instance, a common cause of sepsis is gram-negative bacterial infection. The outer membrane of gram-negative bacteria harbors lipopolysaccharides (LPS) that can trigger an inflammatory reaction in the body during infections, potentially leading to lung damage.[19,20]

Pathogenesis

The development of ALI is highly intricate, involving multiple mechanisms such as inflammation activation,[6] cell apoptosis,[21] oxidative stress injury,[22] and coagulation dysfunction.[23] It is widely believed that at the core of its pathogenesis is an uncontrolled inflammatory response. The initiation of inflammatory cells and the ensuing discharge of various inflammatory agents in ALI prompted by LPS inflict damage on the alveolar-capillary barrier disruption results in heightened permeability. This pernicious cycle ultimately advances into pulmonary fibrosis, lung injury, and lung edema.[24]

Signaling Pathways

The inflammatory response during ALI has been shown by recent studies to involve various signaling pathways like AMPK, Wnt/β-catenin, RhoA/ROCK, JAK/STAT, NF-κB, VEGF, PI3K/Akt, and MAPK.(Figure 1).

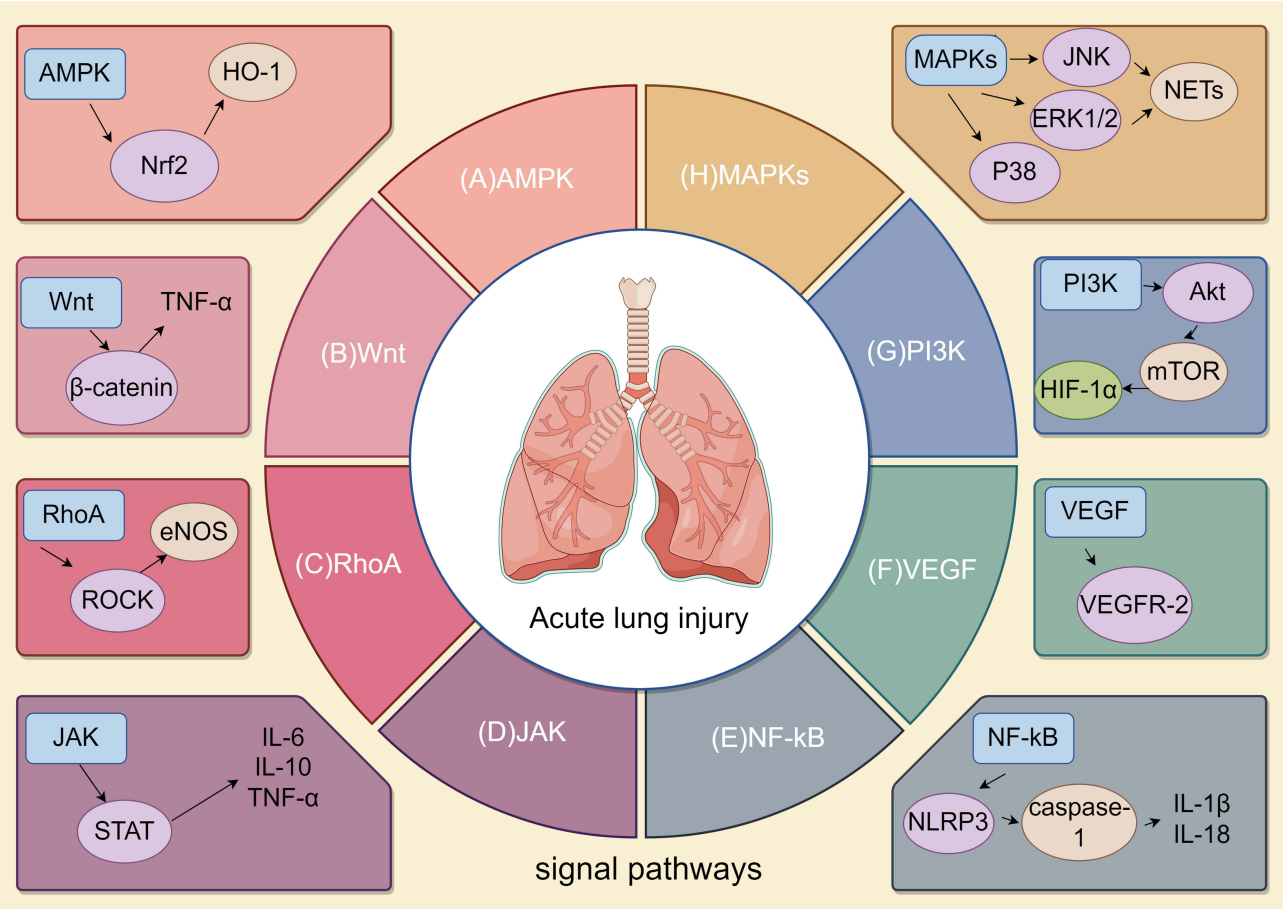

Figure 1 Signaling pathways implicated in acute lung injury. (**A**) AMPK - Nrf2 - HO-1; (**B**) Wnt - β-catenin - TNF-β; (**C**) RhoA - ROCK – eNOS; (**D**) JAK - STAT- IL-6, IL-1β, TNF-α; (**E**) NF-kB - NLRP3 - caspase-1 - IL-1β, IL-18; (**F**) VEGF - VEGFR2; (**G**) PI3K - Akt - mTOR - HIF-1α; (**H**) MAPKs - JNK - NETs; MAPKs - ERK1/2 - NETs; MAPKs - P38.
Abbreviations: AMPK, AMP-activated protein kinase; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; HO-1, heme oxygenase-1; TNF-β, tumor necrosis factor-β; ROCK, Rho-associated kinase; Enos, Endothelial Nitric Oxide Synthase; JAK, anus kinase; STAT, signal transducer and activator of transcription; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, tumor necrosis factor-α; NF-Kb, nuclear factor kappa-B; NLRP3, NOD like receptor heat protein domain related protein 3; IL-18, Interleukin-18; VEGF, Vascular Endothelial Growth Factor; VEGFR2, Vascular Endothelial Growth Factor Receptor 2; PI3K, phosphoinositide 3 kinase; Akt, Protein Kinase B; mTOR, mammalian target of rapamycin; HIF-1α, hypoxia inducible factor-1α; MAPKs, mitogen activated protein kinases; JNK, c-Jun N-terminal kinase; NETs, neutrophil extracellular traps; ERK1/2, extracellular signal-regulated kinase.

AMPK Signaling Pathway

The AMP-activated protein kinase (AMPK) regulates cellular energy metabolism, ensuring energy balance is maintained during metabolic stress.[25] The transcription regulator nuclear factor erythroid 2-related factor 2 (Nrf2) is involved in the antioxidant response. In particular, it regulates heme oxygenase-1 (HO-1) expression. Nrf2 acts downstream of AMPK. Activation of Nrf2 and HO-1 by AMPK suppresses reactive oxygen species production.[26] Studies have shown that Xanthohumol enhances AMPK-Nrf2 pathway to mitigate LPS-induced ALI in mice.[27]

Wnt/β-Catenin Signaling Pathway

Wnt family constituents are glycoproteins that exert their action via autocrine or paracrine modes. Wnt interacts with cell surface-specific receptors, triggering a cascade of protein phosphorylation and dephosphorylation events, which result in nuclear β-catenin accumulation.[28] Many biological processes such as cellular growth, maturation, programmed cell death, motility, penetration, and tissue system balance depend on the Wnt/β-catenin signaling pathway.[29] Villar J. et al[30] reported that the Wnt/β-catenin signaling pathway experienced heightened activation in animals suffering from sepsis-triggered ALI. Moreover, defensive MV repressed WNT/β-catenin signaling pathway and enhanced pulmonary restoration.

RhoA/ROCK Signaling Pathway

The RhoA, a diminutive GTPase protein belonging to the Rho family, represents a key component known as the Ras homologous gene family member A. The Rho-Associated Protein Kinase (ROCK) functions as a downstream effector of RhoA. The Rho/ROCK signaling pathway is involved in cell growth, maturation, movement, and evolution.[31] Endothelial NO synthase (eNOS) can mediate LPS-induced RhoA activation, resulting in pulmonary dysfunction and pro-inflammatory cytokine secretion. Blocking eNOS activity can suppress NF-κB signal transduction.[32] Research has demonstrated the engagement of the Rho/ROCK signaling cascade serves as a mediator for increased permeability in pulmonary endothelial tissues, and it holds a vital role in the pathophysiological progression of ALI.[33]

JAK/STAT Signaling Pathway

Janus kinase (JAK) is an intracellular tyrosine kinase that plays a crucial role in signal transduction initiated via multiple membrane receptors. The JAK/STAT signaling cascade governs a myriad of cell functions that are vital for maintaining internal equilibrium.[34] It also contributes to the emergence of a wide array of inflammatory and autoimmune disorders.[35] Zhang et al[36] showed that during sepsis, LPS upregulates JAK/STAT expression, interacting with Toll-like receptors to cause the excretion of IL-10, IL-6, and TNF-α, resulting in alveolar epithelial and vascular endothelial cell injury, leading to diffuse ALI.

NF-kB Signaling Pathway

NF-κB acts as a transcriptional activator, spurring the creation of cytokines and enhancing cellular longevity. NF-κB exists in nearly every type of animal cell, engaging in cellular reactions to stimuli, such as cytokines, stress, oxidative LDL, free radicals, and viral antigens or bacterial.[37] Several investigations have demonstrated that ALI is linked to the start and activation of NLRP3 inflammasomes, which damage and inflame the lungs via the NF-kB pathway. The subsequent triggering of caspase-1 leads to the release and development of IL-1β and IL-18, which drive cell apoptosis and inflammatory reactions, thus aggravating ALI.[38–44]

VEGF Signaling Pathway

The angiogenic stimulant vascular endothelial growth factor (VEGF) encourages the expansion of endothelial cells. It stimulates the proliferation, increases the permeability, and enhances endothelial cell migration.[45] Research has indicated that pulmonary VEGF upregulation plays a crucial part in lung damage caused by fat embolism. VEGF expression is increased in several forms of ARDS, and its severity is associated with mortality. VEGFR-2 antagonists can significantly alleviate lung inflammation and cellular damage induced by fat embolisms.[46]

PI3K/Akt Signaling Pathway

The PI3K/AKT cascade functions as an internal messenger system that reacts to external cues, enhancing cellular metabolism, division, survival, development, and the formation of new blood vessels.[47] In addition, the PI3K/Akt signaling pathway performs a vital function in cellular survival and resistance to oxidative stress during pulmonary inflammation.[48] Li et al[49] revealed that within mature dendritic cells, HMGB1 triggers the PI3K/Akt/mTOR signaling cascade, upregulating the mRNA levels and subsequent activation of PI3K, Akt, and mTOR to facilitate the development of lung inflammation in ALI.

MAPK Signaling Pathway

Mitogen activated protein kinase (MAPK) comprises p38, ERK and JNK subfamilies, which are key regulatory factors in cell physiology and the pathogenesis of various diseases, including cancer, where they regulate cell proliferation, growth, and apoptosis.[50] Neutrophil extracellular traps (NETs) indirectly induced by LPS cause acute lung injury.[51] Erythropoietin may provide relief from acute lung injury resulting from ischemia-reperfusion by inhibiting the p38 MAPK signaling pathway.[52] FK866 can partially inhibit the JNK pathway and decreases reactive oxygen species production in neutrophils, thereby suppressing NETs.[53] Redouning improves ALI by obstructing the phosphorylation process of ERK1/2 and the formation of NETs.[54]

NLRP3 Inflammasome

Overview

Innate immunity acts as the initial defense mechanism against the incursion of pathogens. Unlike the adaptable branch of the immune system, it has nonspecific defense functions.[55] Innate immunity comprises two lines. The first one includes natural barriers effectively prevent the invasion of common pathogens into tissue.[56] The second line consists of leukocytes, which eliminate pathogens upon detection.[57] Pattern recognition receptors (PRRs) expressed in germ cells are primarily responsible for the primary stimulation of inherent immune responses. PRRs can detect the presence of microbes by recognizing conserved pathogen macromolecular structures, known as pathogen-associated molecular patterns (PAMPs). They are also capable of recognizing endogenous substances secreted by compromised cells, commonly known as damage-associated molecular patterns (DAMPs).[58] In response to infection, PRRs activate signaling pathways, thereby stimulating the host defense response against microbial invasion.[59] PRRs can be classified into numerous categories, which encompass TLRs, RIG-I-like receptors, and nucleotide-binding oligomerization domain receptors and leucine-rich repeat-containing receptors (NLRs), synthase of cyclic GMP-AMP and the route that activates interferon genes, along with AIM2-similar receptors and C-type lectin.[60] When these PRRs are activated, they can initiate an inflammatory reaction to combat infections and heal tissue injuries. Through these mechanisms, innate immunity plays ensures an effective response to harmful external stimuli.

Intracellular pattern recognition receptors (PRRs) orchestrate the assembly of inflammasomes, which are intricate multi-protein structures.[61] Once assembled, inflammasomes can trigger the enzymatic activity of caspase-1 advances the development and release of IL-1β and IL-18, in addition to cleaving gasdermin-D (GSDMD) and thus facilitating cellular pore formation and subsequent pyroptosis.[62] The NLRP3 is the most thoroughly examined inflammasome.[63] It is primarily expressed in macrophages and neutrophils. Abnormal NLRP3 inflammasome activation can cause inflammatory ailments.[64]

Composition of the NLRP3 Inflammasome

The effector enzyme caspase-1, adaptor ASC (sometimes referred to as PYCARD), and sensor NLRP3 make up the NLRP3 inflammasome.[65] The NLRP3 molecule is composed of three unique segments: an N-terminal pyrin domain, a NACHT domain situated centrally, and a C-terminal domain that is characterized by a series of leucine-rich repeats. The NACHT domain plays a pivotal role in driving ATPase activity, an essential mechanism for the self-assembly and operational efficacy of NLRP3.[66] This domain is also a major structural component of the inflammasome. ASC is comprised of two integral components: the PYD domain, which associates with NLRP3, and the CARD domain, which facilitates its connection to caspase-1.[67] The effector caspase-1 of the NLRP3 inflammasome converts IL-1β and IL-18 precursors into their activated forms.[68] Caspase-1 plays a pivotal role in cell death associated with inflammation, specifically through a process known as pyroptosis.[69]

NLRP3 Inflammasome activation

The initiation of NLRP3 inflammasome entails a dual approach: firstly, a preparatory phase, and secondly, the actual triggering event.[70] The NLRP3 inflammasome activation entails four typical pathways: ion channels, mitochondrial autophagy, excessive reactive oxygen species (ROS) production and lysosomal rupture.[71]

Priming of the NLRP3 Inflammasome

During the priming phase, immune cells must be exposed to inducing stimuli such as LPS and tumor necrosis factors, which bind to transmembrane PRRs such as IL-1R, TLRs, and TNFR. This binding activates NF-kB, further upregulating the expression of inflammasome components NLRP3 and pro-IL-1β. The presence of high levels of NLRP3 and pro-IL-1β is crucial for inflammasome formation.[72]

Activation of the NLRP3 Inflammasome

Upon the first signal, NLRP3 is stimulated by diverse activators including inherent DAMPs, assorted PAMPs, multiple pathogens, and potassium ions.[73] The structural proteins of NLRP3 bind to the PYD of the adaptor ASC through oligomerization. Next, the CARD domain within ASC interacts with the CARD in pro-caspase-1, culminating in the formation of the fully integrated NLRP3 inflammasome, and thereby converting pro-caspase-1 to its active form caspase-1. IL-1β and IL-18 mature as a result of caspase-1 activation, and GSDMD is cleaved into its N- and C-terminal components.

The GSDMD N-terminus can form pores by binding to the cell membrane, thus promoting the secretion of pro-inflammatory cytokines (IL-1β and IL-18), which in turn, initiates pyroptotic cell death. (Figure 2).[74,75]

NLRP3 Inflammasome and ALI

There is considerable proof highlighting the crucial function of the NLRP3 inflammasome in ALI.[38] It has been demonstrated through research that patients suffering from ARDS often exhibit increased concentrations of IL-1β and IL-18, markers that typically correlate with unfavorable outcomes.[39] Injection of extracellular mitochondrial DNA into the trachea of mice, NLRP3 inflammasome is promoted through the TLR9, p38MAPK, and NF-κB pathways, which leads to increased expression of NLRP3, ASC, and caspase-1. This in turn stimulates IL-1β and IL-18 release to cause lung injury.[40] In a murine model of LPS-induced septic ALI, IL-1β and IL-18 concentrations in bronchoalveolar lavage fluid (BALF) and lung tissue were markedly elevated, coinciding with an uptick in the activity of NLRP3 and caspase-1.[41] The upregulation of inflammatory cytokines IL-18, IL-1β, and TNF-α is observed in ALI induced by sepsis, indicating that Activation of NLRP3 inflammasome stimulates generation of proinflammatory cytokines, and its manifestation is correlated positively with disease severity and fatality.[42] In ventilator-induced lung damage, TLR4 activation activates NLRP3 inflammasome, thereby promoting inflammatory damage. Further, NLRP3 knockout significantly alleviates ventilator-induced lung injury.[43,44] In summary, Numerous investigations have indicated a close link

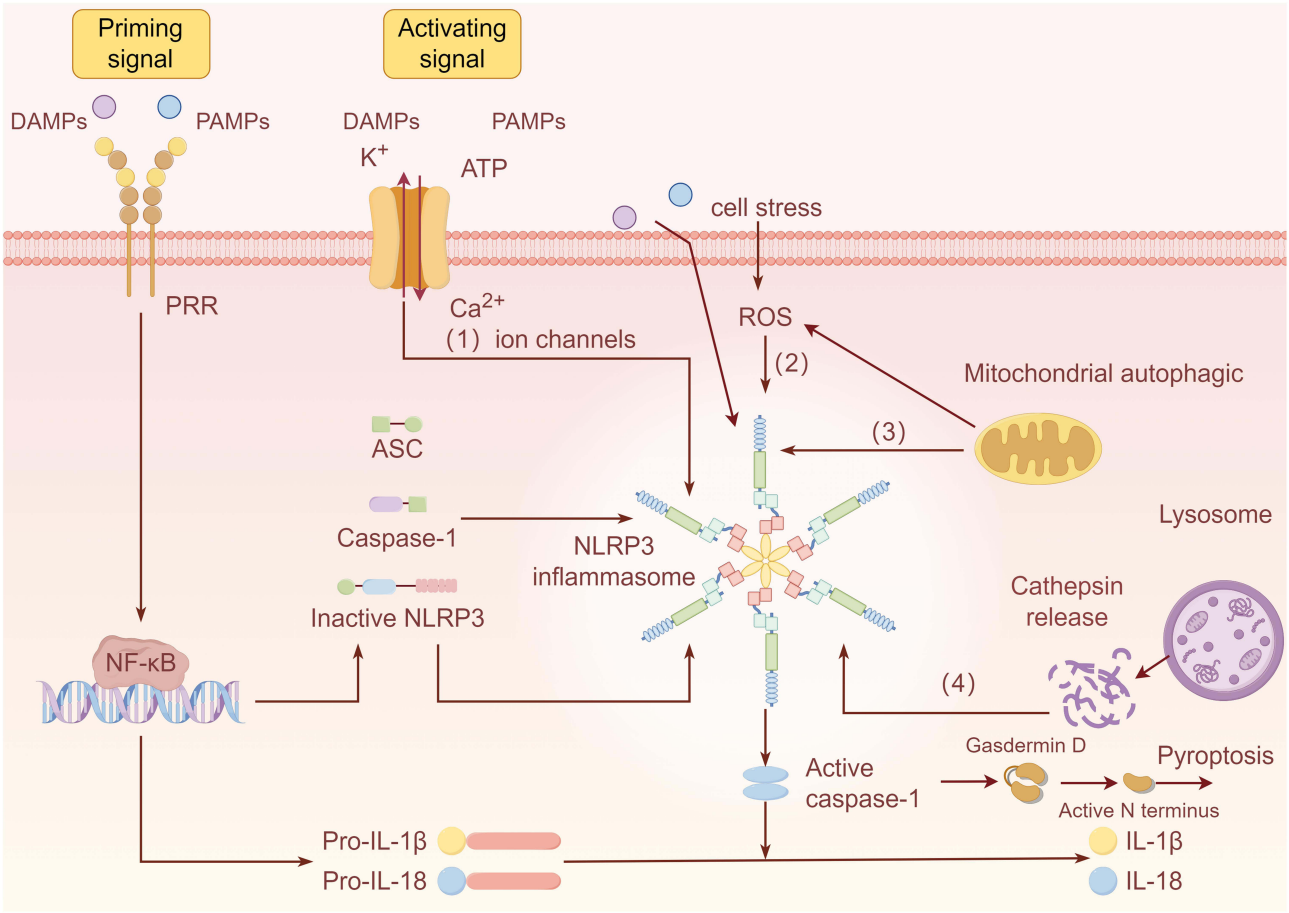

Figure 2 Mechanisms of NLRP3 inflammasome activation. The activation of NLRP3 inflammasome occurs via four classical pathways: (1) ion channels; (2) excessive production of reactive oxygen species; (3) mitochondrial autophagy, and (4) lysosomal rupture. Activation of the NLRP3 inflammasome occurs in two phases. In the priming phase, a stimulus binds to pattern recognition receptors and activates NF-kB to further upregulate the expression of NLRP3, pro-IL-1β, and pro-IL-18. In the activation phase, the structural protein NLRP3 binds to the PYD of ASC through oligomerization, whereafter the CARD of ASC binds to the CARC of pro-caspase-1 to form the intact NLRP3 inflammasome. The NLRP3 inflammasome then activates pro-caspase-1, which in turn promotes the maturation of IL-1β and IL-18, in addition to cleaving Gasdermin-D to N- and C-terminal fragments, with the activated N terminus promoting pyroptosis.

between ALI and the NLRP3 inflammasome. Targeted suppression of NLRP3 inflammasome and related signaling pathways represents a new direction in ALI prevention and treatment research.

Therapeutic Approaches

Research on ways to produce anti-inflammatory medications that hinder the NLRP3 inflammasome activation has become a focal point of interest in recent research. Given the link between ALI and the NLRP3 inflammasome, targeting NLRP3 for inhibition has increasingly become a pivotal approach in the therapeutic intervention for ALI.

Inhibiting the NF-kB Pathway

Propofol is a commonly used drug for anesthesia induction and maintenance. Propofol is also known to harbor anti-cancer,[76] antioxidant,[77] neuroprotective,[78] and anti-inflammatory activities.[79] Prior research has demonstrated that propofol influences pulmonary damage. Exposure to sevoflurane and propofol exhibits anti-inflammatory properties in the context of LPS-triggered ALI.[80] Propofol has been shown to reduce inflammation and oxidative stress by inhibiting the p38 MAPK/NF-κB pathway and NLRP3 inflammasome activation, as well as to alleviate LPS-induced pulmonary edema in neonatal rats. Propofol effectively reversed the effects of LPS treatment on the NLRP3 inflammasome and the p38 MAPK/NF-κB pathway in newborn rats.[81] Propofol may thus be a prospective medication for the therapy of newborn ALI.

Metformin is an established and effective anti-diabetic drug. It additionally demonstrates protective benefits for the lungs across various acute lung injury scenarios,[82] PM2.5-induced[83] and endotoxemia-induced pulmonary injury.[84] Its action may include the activation of AMP-activated protein kinase (AMPK) to suppress NF-κB in endothelial cells and consequently inhibit cytokine-induced inflammation and adhesion factor expression.[85] That is, metformin mitigates LPS-triggered ALI by inhibiting endothelial cell pyroptosis by suppressing the NF-κB-NLRP3 signaling pathway. Throughout the progression of inflammatory lung injury induced by LPS, the pulmonary endothelium undergoes impairment, rendering it unable to effectively maintain a protective barrier. Metformin effectively counteracts the negative repercussions by reversing them, thus safeguarding the endothelial pathways and ameliorating lung function.[86] Glibenclamide also has the ability to reduce LPS-induced ALI damage.[87]

As an anti-inflammatory agent, berberine has therapeutic effects in many diseases. Berberine modulates the NF-κB signaling pathway, exhibiting anti-inflammatory properties.[88] It can suppress the triggering of the NLRP3 inflammasome by the influenza virus in macrophages by enhancing mitochondrial autophagy and reducing mitochondrial ROS, thus mitigating lung damage.[89] Moreover, berberine has the ability to inhibit the interaction of NLRP3 with NEK7, resulting in a direct and effective anti-inflammatory response.[90] Berberine treatment down-regulated p-NF-κB, further suppressing NLRP3 levels in vivo and in vitro. This caused a marked reduction in IL-18 and IL-1β concentrations in pulmonary tissues, considerably alleviating inflammation.[91] These results underscore the promising role that berberine could play in treating ALI.

Glycyrrhizic acid is renowned for its excellent pharmacological effects and various biological activities, including antiviral and anti-inflammatory properties.[92] Glycyrrhizic acid can reduce the production of IL-Iβ and TNF-α in inflammation, inhibiting NF-κB activation.[93] Furthermore, it may thwart colorectal cancer development by disrupting the HMGB1-TLR4-NF-κB signaling cascade.[94] Glycyrrhizic acid modulates autophagy through the PI3K/AKT/mTOR pathway to improve LPS-induced ALI.[95] It possesses the capability to modulate the signaling cascade of the NF-κB/NLRP3 inflammasome, hence curtailing the inflammatory reaction instigated by LPS.[96] To sum it up, glycyrrhizic acid may alleviate ALI by suppressing the NF-kB pathway, positioning it as a potential therapeutic agent.

Remarkably, it has also been demonstrated that LPS-induced acute lung injury can be relieved by isochlorogenic acid A,[97] pterin,[98] and hederasaponin-C[99] through modification of the NF-κB-NLRP3 signal pathways.

Inhibiting Excessive Production of ROS

Oxidative stress, coupled with the ensuing inflammation, are key underlying pathological mechanisms in ALI. Emodin, an active constituent of Rhubarb, has anti-inflammatory characteristics. Studies have shown that emodin can improve LPS-induced ALI.[100,101] Furthermore, emodin has the ability to suppress ROS, MPO, and MDA generation. In addition,

emodin guards against ALI brought on by LPS, presumably by lowering ROS generation and suppressing NLRP3 expression.[102] Emodin therefore represents a prospective medical remedy for ALI and lung inflammation.

Nrf2 occupies a pivotal role as a transcription factor in the antioxidant response, and it comes into action by inhibiting oxidative stress and inflammation.[103] Recent research indicates that Nrf2 can prevent activation of the NLRP3 inflammasome.[104] Numerous substances possess the ability to alleviate LPS-triggered ALI through Nrf2 downregulation of NLRP3 inflammasome-induced cellular apoptosis. Among them, honokiol, a compound extracted from the Magnolia officinalis tree, is known for its abilities to combat oxidative stress and inflammation. HKL markedly increases the protein and mRNA levels of Nrf2 and HO-1, reduces MPO and MDA levels, and boosts SOD levels in vivo and in vitro. Moreover, Nrf2 knockdown can reverse the antioxidant effect of HKL, indicating that the latter exerts its antioxidant effect in LPS-induced ALI via Nrf2/HO-1 signaling.[105] Oridonin (Ori), a natural substance with antioxidant and anti-inflammatory effects extracted from Rabdosia rubescens, serves as an activator of Nrf2. It can reduce LPS-triggered inflammation through the NF-κB pathway.[106] In addition, it generates a covalent connection with cysteine 279 situated in the NACHT domain of NLRP3, thus impeding the interaction and activation of the NLRP3 inflammasome by hindering the link between NLRP3 and NEK7.[107] Overall, Ori delivers protective benefits against LPS induced acute lung injury by activating its anti-inflammatory and antioxidant responses through the Nrf2 pathway. Moreover, compounds such as melatonin,[108] hydnocarpin D,[109] isoorientin,[110] citrulline,[111] and glycyrrhizic acid[95] also inhibit NLRP3 inflammasome-mediated cell apoptosis through Nrf2, reducing LPS-induced ALI.

Inhibiting Mitochondrial Autophagy

Mitochondrial autophagy is notably related to NLRP3 inflammasome activation.[112] Sestrin2 (Sesn2), a highly conserved stress-induced protein, plays a vital part in regulating cellular stress reactions and antioxidant protection.[113] Studies have shown that Sesn2 can prevent sepsis by inducing mitochondrial autophagy and suppressing NLRP3 activation in macrophages.[114] Moreover, Sesn2 has the ability to inhibit the NLRP3 inflammasome's activation, which is typically instigated by LPS within pulmonary macrophages, reducing cell apoptosis and protecting mitochondria from damage. Sesn2 maintains mitochondrial homeostasis in macrophages through the Pink1/Parkin signaling pathway during mitochondrial autophagy, ultimately protecting the lungs from LPS-induced ALI.[115] These discoveries validate Sesn2 as a fresh therapeutic focus for managing ALI/ARDS.

Inhibiting Ion Channels

Calcium, a crucial intracellular secondary messenger, plays a role in several cellular mechanisms.[116] The influx of calcium ions is recognized to contribute to NLRP3 inflammasome activation.[117] The binding of calcium to calmodulin (CaM) leads to activation of CaM kinase (CaMK), which initiates inflammation.[118] In alveolar type II epithelial cells, CaMK4 is essential for initiating the NLRP3 inflammasome, which exacerbates lung damage in mice with LPS-induced ALI. The drug KN-93, a CaMK4 inhibitor, can effectively improve ALI by inhibiting NLRP3 inflammasome activation.[119] Thus, inhibiting CaMK4 could represent a new approach for treating ALI.

Inhibiting the Maturation and Secretion of IL-1β and IL-18

The NLRP3 inflammasome coordinates IL-1β and IL-18 processing and secretion. Blocking IL-1β and IL-18 production or upstream signaling may be effective in treating ALI/ARDS.[120] Rapamycin, a natural product with immunosuppressive effects widely used in patients who undergo organ transplantation,[121] has been confirmed to suppress autophagy by inhibiting mTOR an thus regulating the production of IL-1β and IL-18.[122] The induction of autophagy can limit the secretion of IL-1β and IL-18 by clearing damaged mitochondria and preventing the release of mitochondrial ROS.[123,124] Therefore, rapamycin-induced autophagy helps to reduce the generation of IL-1β and IL-18 after LPS exposure. It has also been demonstrated that rapamycin treatment reduces the total number of cells as well as the neutrophil count in BALF after an LPS infection.[125,126] Further, rapamycin shields mice from lung damage triggered by LPS by suppressing mTOR activity, which subsequently reduces IL-1β and IL-18 production, suppressing immune cell infiltration.[127] Therefore, rapamycin may represent an effective drug for treating ALI (Table 1).

Table 1 Summary of Drugs That Inhibit the NLRP3 Inflammasome for the Treatment of Acute Lung Injury

Therapeutic Approaches	Therapeutic Drug	Reference
Inhibiting the NF-kB Pathway	Propofol	[80,81]
	Metformin	[82–86]
	Glibenclamide	[87]
	Berberine	[88–91]
	Glycyrrhizic acid	[93–96]
	Isochlorogenic acid A	[97]
	Pterin	[98]
	Hederasaponin-C	[99]
Inhibiting the Excessive Production of ROS	Emodin	[100–102]
	Honokiol (HKL)	[105]
	Oridonin (Ori)	[106,107]
	Melatonin	[108]
	Hydnocarpin D	[109]
	Isoorientin	[110]
	Citrulline	[111]
	Glycyrrhizic acid	[95]
Inhibiting Mitochondrial Autophagy	Sestrin2 (Sesn2)	[113–115]
Inhibiting Ion Channels	KN-93	[119]
Inhibiting the Maturation and Secretion of IL-1β and IL-18	Rapamycin	[121–127]

Summary

Herein, we reviewed the progress in our understanding of ALI and the configuration and stimulation of NLRP3 inflammasome, and explored the NLRP3 inflammasome's mechanism and potential therapeutic approaches in ALI. The NLRP3 inflammasome has the potential to be an ideal candidate for early detection and treatment of ALI owing to its crucial functions in transducing signals and releasing pro-inflammatory cytokines. Future investigations ought to prioritize the identification of upstream factors that affect the NLRP3 inflammasome and the development of interventions aimed at its assembly. Taken together, targeting NLRP3-driven inflammation may represent an important direction to treat and prevent ALI.

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Disclosure

The authors report no conflicts of interest in this work.

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