Mechanisms and therapeutic strategies of pyroptosis in sepsis-induced acute lung injury (Review)

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Abstract. Sepsis-induced acute lung injury (S-ALI) is a leading cause of respiratory failure and mortality in intensive care units, characterized by profound biological and clinical heterogeneity that explains the repeated failure of uniform anti-inflammatory therapies. This variability underscores the urgent need for mechanism-based patient stratification and precision medicine approaches. Pyroptosis, a regulated inflammatory cell death program driven by gasdermin-mediated membrane pore formation, has emerged as a critical driver of alveolar-capillary barrier disruption and cytokine amplification in S-ALI. The activation of canonical and non-canonical inflammasome pathways, together with molecular crosstalk within the integrated PANoptosome network, promotes context-dependent pyroptotic responses across pulmonary endothelial, epithelial and immune cells. Notably, recent insights into lineage plasticity and transcriptional heterogeneity further elucidate the dynamic cellular orchestration of these pathways. Pyroptotic effectors, such as circulating gasdermin D fragments and mature IL-1β/IL-18, are detectable in patients with sepsis and acute respiratory distress syndrome, being associated with hyperinflammatory endotypes, disease severity and clinical trajectories. By integrating preclinical mechanistic insights with emerging human biomarker and trial data, the present review positions pyroptosis as a clinically actionable, stratification-relevant target. The present review highlights current advances in pathway-specific inhibitors and discusses their potential to enable biomarker-guided, personalized interventions in critically ill patients.

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Abbreviations: ALI, acute lung injury; CLP, cecal ligation and puncture; C5a, complement component 5a; C5aR, complement component 5a receptor; DAMPs, damage-associated molecular patterns; GSDME, gasdermin E; GSDMD, gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; LPS, lipopolysaccharide; MSCs, mesenchymal stem cells; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; S-ALI, sepsis-induced acute lung injury; TNF-α, tumor necrosis factor-α

Key words: sepsis, acute lung injury, pyroptosis, inflammasome, gasdermin, precision medicine, targeted therapy

Contents

1. Introduction

Sepsis is a multi-organ dysfunction syndrome that occurs following infection in the human body. It is a disease with extremely high morbidity and mortality rates worldwide (1-5). Among the multiple organs involved in the complications of sepsis, the lungs are the earliest target organ to be invaded and damaged, and the most likely organ in which sepsis occurs (2-6). Studies have shown that ~25-45% of patients with sepsis

may develop acute lung injury (ALI) (2-5,7). Globally, sepsis affects tens of millions of patients annually, with a substantial proportion developing pulmonary complications, such as ALI. Once complicated by ALI, mortality is substantially elevated, with attributable mortality from ALI in patients with sepsis being around ~12-37% and overall mortality often in the 30-50% range, depending on disease severity and setting. In the intensive care unit (ICU), these patients often present with heterogeneous clinical courses, with responses to standard supportive therapy varying markedly (2-5,8). This pronounced biological and clinical variability, reflecting distinct underlying endotypes, explains the repeated failure of large-scale randomized controlled trials that evaluated uniform 'one-size-fits-all' anti-inflammatory interventions. Emerging evidence suggests that sepsis-induced ALI (S-ALI) may be broadly stratified into at least two clinically relevant inflammatory subphenotypes, including a hyperinflammatory pyroptosis-high endotype and a relatively immunosuppressed or hypo-inflammatory endotype. The hyperinflammatory subtype is typically characterized by excessive inflammasome activation, elevated circulating gasdermin D (GSDMD)-N-terminal (NT) levels, the increased release of interleukin (IL)-1β and IL-18, and amplified innate immune signaling, whereas the immunosuppressed subtype is associated with attenuated cytokine responses, immune exhaustion, and reduced inflammatory reactivity (2-5,9). These endotypes may be identified through biomarker-guided stratification strategies integrating plasma GSDMD fragments (GSDMD-NT >120 ng/ml), IL-18, IL-1β and inflammasome-associated signaling signatures, thereby enabling the more precise selection of patients who may benefit from pyroptosis-targeted interventions (2-5). This consistent therapeutic failure underscores the urgent need for a transition from non-specific symptomatic support to precision-guided, mechanism-driven strategies in future ICU management. The main manifestation of ALI is the massive infiltration of inflammatory response factors and mediators, which leads to the destruction of the alveolar endothelial barrier. The release of these substances by inflammatory cells further activates effector T-cells and alveolar epithelial cells. The massive inflammatory exudate leads to increased alveolar perfusion load, seriously affecting alveolar ventilation and gas exchange functions, thus leading to decreased respiratory function (2-5,10). Currently, the primary treatment for sepsis-induced ALI relies on antibiotics and symptomatic supportive care, which often fail to address the specific molecular executioners driving individual disease trajectories in critically ill patients (2-5,11). This highlights the necessity of integrating deep pathophysiological insights into individualized ICU strategies to overcome the limitations of traditional, broad-spectrum therapies.

The pathogenesis of S-ALI is complex, involving multiple interconnected mechanisms, including inflammation, oxidative stress, coagulation dysfunction and the gut-lung axis (2-5,12) (Fig. 1). In the early stages of sepsis, pro-inflammatory cytokines and immune mediators are rapidly released, triggering endothelial dysfunction and increased pulmonary capillary permeability (2-5,13). This leads to the leakage of protein-rich fluid into the alveolar space, causing pulmonary edema (2-5,14). The resulting disruption of the alveolar-capillary barrier, which directly impairs gas exchange and triggers the characteristic hypoxemia of ALI, represents the primary clinical phenotype of S-ALI (Fig. 2) (2-5,15). Although scientists continue to acquire a more in-depth understanding of the pathophysiology of ALI, the pathophysiology of S-ALI remains complex, involving multiple molecular pathways and cell types (2-5,16). Currently, clinical treatment primarily involves early infection control, optimized mechanical ventilation and supportive care for vital organs (2-5,17). However, existing treatment options are ineffective in reducing mortality rates and may lead to complications, such as ventilator-associated pneumonia and barotrauma (2-5,18,19). Identifying the specific molecular mechanisms that drive patient-specific disease trajectories is therefore critical for the development of next-generation ICU interventions and personalized therapeutic approaches.

Pyroptosis is a highly regulated programmed cell death process that has emerged as a critical, actionable driver of inflammatory amplification in S-ALI (2-5,20,21). Pyroptosis, also known as inflammatory cell death, is a mode of programmed cell death that is dependent on cysteine aspartate-specific protease-1 (caspase-1) (2-5,21,22). Unlike apoptosis and autophagy, pyroptosis is characterized by triggering an intense inflammatory response via gasdermin-mediated membrane pore formation (2,3,5,21,23). Although initially considered to be a host-protective mechanism, recent studies have demonstrated that excessive systemic cellular pyroptosis in the context of sepsis accelerates the release of inflammatory markers in immune cells (5,21,24,25), endothelial cells and epithelial cells, leading to systemic organ tissue damage (5,26,27). This dysregulated pyroptotic activity accounts for a substantial portion of the biological heterogeneity in patients with sepsis, highlighting why non-targeted therapies often fail; this emphasizes the need for precision-guided interventions in ICU care.

Therefore, targeting pyroptosis has emerged as a novel precision strategy for the treatment of sepsis and its pulmonary complications (5,28). Inhibiting key pyroptotic mediators may suppress uncontrolled lysis and prevent further organ injury (5,29). Existing inhibitors of pyroptosis, such as nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) or caspase-1 antagonists and natural anti-inflammatory compounds, have demonstrated the potential for attenuating the effects of pyroptosis in preclinical models (5,30-32). These findings provide a translational roadmap for integrating pyroptosis-targeted interventions into individualized ICU care, allowing for the selection of specific therapies based on the unique molecular signatures of a patient. A summary of key preclinical and clinical evidence of pyroptosis activation during S-ALI is presented in Table I. Table I presents data from multiple murine models [primarily lipopolysaccharide (LPS)- and cecal ligation and puncture (CLP)-induced S-ALI] demonstrating the elevated expression of pyroptosis-related markers, such as NLRP3, cleaved caspase-1, GSDMD, IL-1β and IL-18 in lung tissues at different time points (e.g., 8-24 h post-induction). Table I also includes human studies demonstrating increased circulating levels of GSDMD p30, NLRP3 and IL-1β/IL-18 in patients with sepsis in the ICU, which are associated with disease severity and poor outcomes.

The NLRP3 inhibitor, MCC950, has been shown to suppress the release of IL-1β and reduce inflammatory

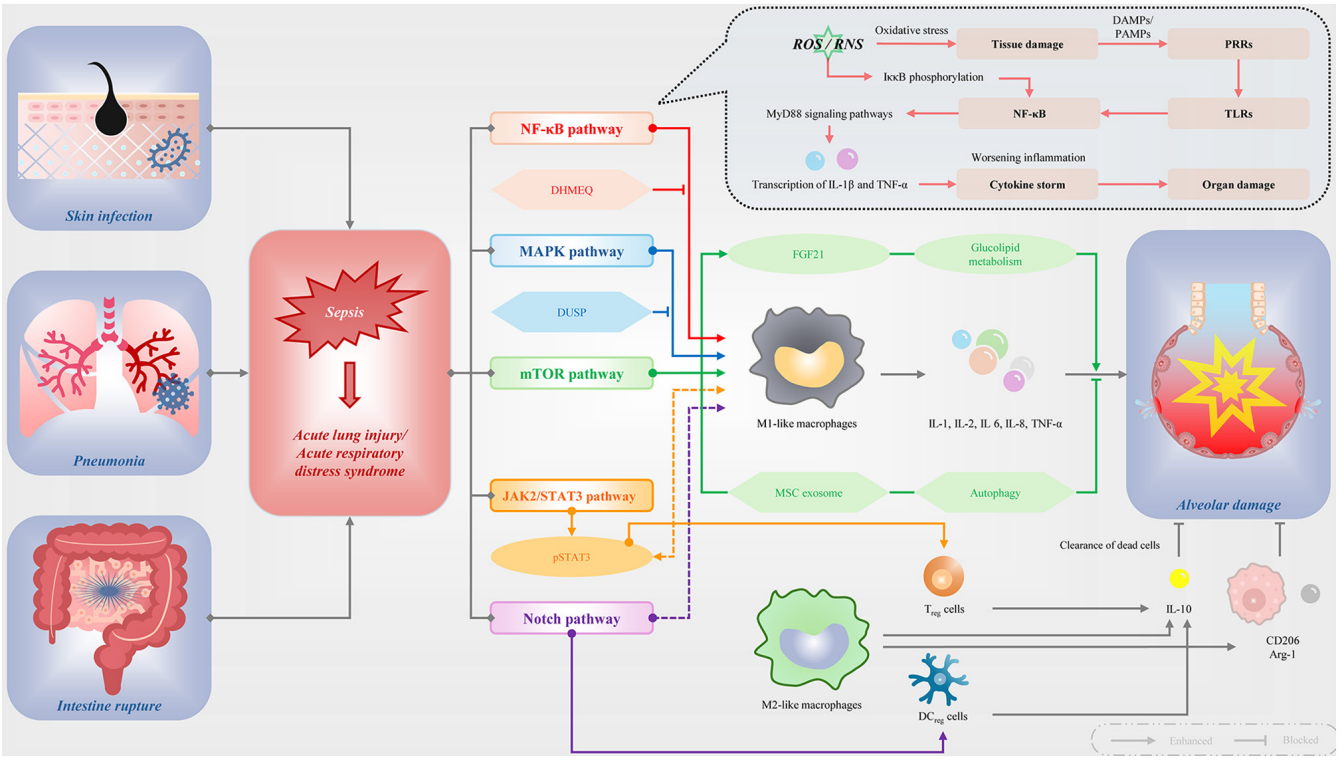

Figure 1. Mechanisms of sepsis-induced ALI/ARDS. Infectious foci such as skin infections, pneumonia and intestinal ruptures can induce sepsis, which in turn leads to the development of ALI/ARDS through multiple inflammatory and immunomodulatory pathways. Exogenous PAMPs and endogenous DAMPs are mediated by PRRs and TLRs, which activate the NF-κB pathway and MyD88-dependent signaling, induce oxidative stress (ROS/RNS) and IκB phosphorylation, and promote IL-1β, IκB and IκB phosphorylation. which promotes the expression of pro-inflammatory factors, such as IL-1β and TNF-α, creating a cytokine storm that ultimately results in alveolar structural destruction and organ damage. The figure was generated using BioGDP.com (BioGDP Scientific Illustration Platform, https://BioGDP.com). PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; MyD88, myeloid differentiation factor 88; ROS, reactive oxygen species; RNS, reactive nitrogen species; IL, intereukin; DHMEQ, Dehydroxymethylepoxyquinomicin; DUSP, dual specificity phosphatases; FGF21, fibroblast growth factor 21.

lung injury in preclinical models (5). Likewise, caspase-1 inhibitors, such as VX-765 have also demonstrated potential in attenuating pyroptosis and protecting against sepsis-induced lung damage (5,33). Blocking GSDMD activation represents another promising strategy to halt pore formation and cytokine efflux, providing a more surgically precise approach than traditional broad-spectrum steroids (5,34).

Pyroptosis is activated by inflammatory vesicles (5,35). Following its activation, it causes cell membrane perforation, cell swelling and rupture by triggering caspase-1 and activating GSDMD, which leads to the marked release of IL-1β and IL-18, triggering a catastrophic inflammatory cascade (5,36). Uncontrolled pyroptosis disrupts epithelial and endothelial barriers, exacerbating lung injury and contributing to the pronounced heterogeneity of the outcomes of patients in the ICU (5,37,38), Notably, pyroptosis shares complex molecular similarities and crosstalk with ferroptosis, apoptosis and necroptosis, and these interactions have historically remdered the development of selectively targeted therapies more complex (Fig. 3) (5,39,40). In addition, while reducing pyroptosis can reduce inflammation, excessive inhibition may suppress essential immune defenses. Determining the optimal therapeutic window for pyroptosis modulation based on biomarker-guided stratification is therefore essential for safe and effective ICU interventions (5,41).

The present review focuses on elucidating the signaling pathways underlying pyroptosis in order to provide a coherent understanding of its molecular mechanisms and regulatory characteristics. The role of pyroptosis in the development and progression of S-ALI is discussed with particular focus on its contribution to inflammatory amplification and tissue damage in critically ill patients. In addition, current advances in strategies aimed at modulating pyroptotic processes are summarized to clarify their potential therapeutic relevance and to identify molecular targets that may support mechanism-guided intervention. By connecting pyroptotic mechanisms with clinical heterogeneity and potential targeted therapies, the present review aimed to provide knowledge of precision-guided ICU strategies and to support the future of individualized critical care.

2. Molecular mechanisms of pyroptosis

The biological heterogeneity observed in patients with S-ALI reflects distinct molecular cascades rather than a uniform inflammatory endpoint (5,42). Multiple members of the caspase family initiate pyroptosis by converging on the proteolytic cleavage of gasdermin proteins, a programmed process characterized by the formation of large transmembrane pores (5,43). This biochemical execution triggers rapid cytoplasmic swelling, osmotic membrane rupture and the massive efflux of inflammatory mediators and intracellular damage-associated molecular patterns (DAMPs) into the alveolar space (5,44). Crucially, the specific caspase-gasdermin axis activated

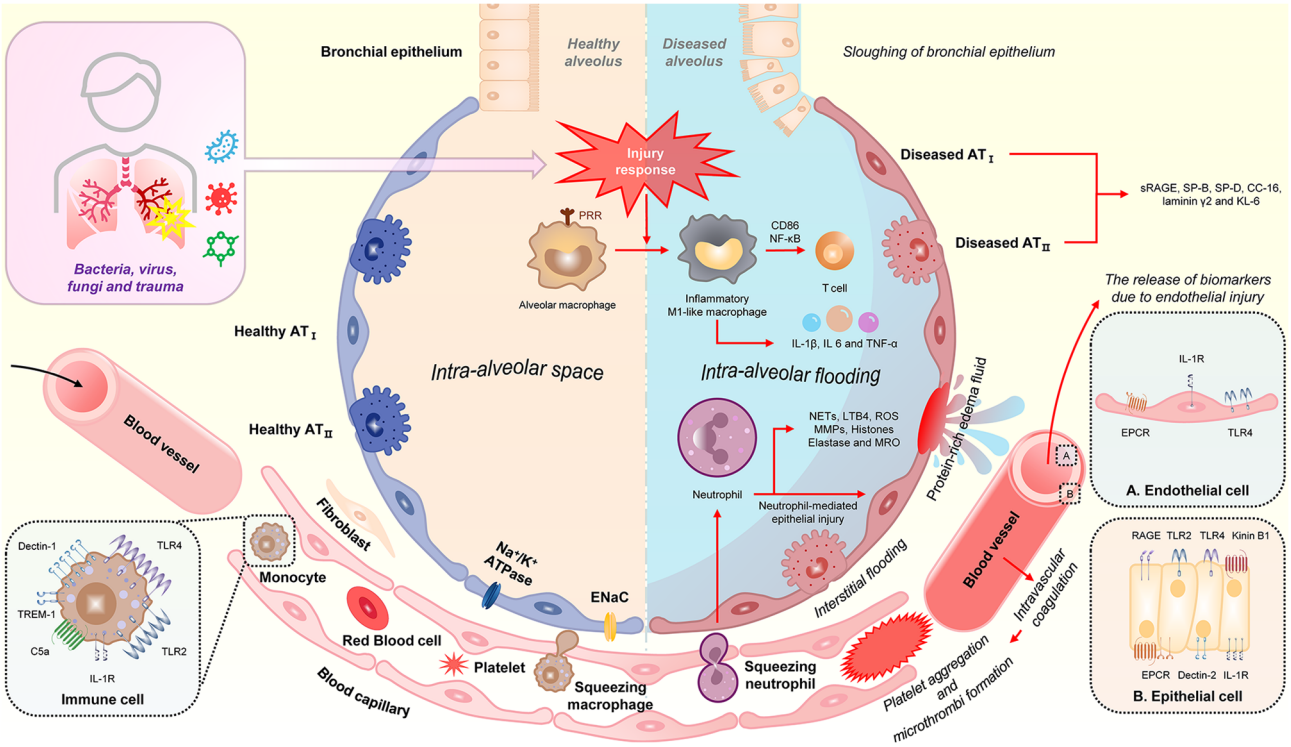

Figure 2. Pathologic mechanisms of sepsis-induced pulmonary vascular injury. Exogenous pathogens and their associated molecules (PAMPs) along with endogenous signals (DAMPs) released by cellular injury activate PRRs, triggering systemic inflammatory responses and oxidative stress. Large amounts of inflammatory mediators and free radicals damage pulmonary vascular endothelial cells, disrupting the tight junctions between endothelial cells and their barrier function, leading to increased vascular permeability. Endothelial dysfunction further causes fluid extravasation, microthrombosis and local circulatory disorders, ultimately exacerbating pulmonary microcirculatory disorders and tissue ischemia. The figure was generated using BioGDP.com (BioGDP Scientific Illustration Platform, https://BioGDP.com). PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; TLR, Toll-like receptor; IL, interleukin; C5a, complement component 5a; TREM-1, triggering receptor expressed on myeloid cells-1; NETs, neutrophil extracellular traps; LTB4, leukotriene B4; ROS, reactive oxygen species; MMPs, matrix metalloproteinases; RAGE, receptor for advanced glycation end products.

within the lung microenvironment dictates the kinetics and magnitude of the pulmonary response, providing a robust molecular framework for defining patient-specific inflammatory endotypes (5,42,45). Currently, four principal signaling pathways have been identified as the primary executors of this programmed cell death: the canonical, noncanonical, apoptotic caspase-mediated, and granzyme-mediated pathways (Fig. 4).

The canonical inflammasome pathway. The canonical pathway represents the most thoroughly characterized mechanism driving pyroptosis in the septic lung. It is initiated when intracellular pattern recognition receptors, such as absent in melanoma 2, pyrin, or various nucleotide-binding oligomerization domain-like receptors (NLRP1, NLRP3 and NLRC4), detect conserved pathogen-associated molecular patterns or endogenous DAMPs released during cellular stress (5,45,46) (Fig. 4A). Unlike stochastic inflammatory triggers, the assembly of the NLRP3-apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC)-caspase-1 inflammasome functions as a high-fidelity molecular amplifier that dictates the intensity of the early pulmonary cytokine storm (47,48). Upon successful assembly of this multiprotein complex, mature caspase-1 processes pro-IL-1β and pro-IL-18 into their bioactive forms, while concurrently cleaving GSDMD to liberate the N-terminal pore-forming domain (GSDMD-NT) (49). In the complex landscape of S-ALI, this pathway serves as the primary engine for early hyper-inflammation and the metabolic priming of the alveolar vascular endothelium (50,51). The significant individual variability in the activation thresholds of these cytosolic sensors explains the inconsistent clinical efficacy of broad-spectrum anti-inflammatory agents, suggesting that patients with a hyper-primed canonical axis require interventions specifically targeting inflammasome assembly rather than downstream effector cytokines (52).

The non-canonical inflammasome pathway. For patients suffering from Gram-negative bacterial sepsis, the noncanonical pathway provides a direct, autonomous sensing mechanism that bypasses the classical receptor-mediated signaling hierarchy (53,54). In this axis, human caspase-4/5 (or murine caspase-11) functions as an intracellular receptor that binds directly to cytosolic LPS, a process significantly facilitated by interferon-inducible guanylate-binding proteins that destabilize pathogen-containing vacuoles (55,56) (Fig. 4B). This direct protein-LPS interaction represents a rapid-response executioner of endothelial lysis, occurring independently of the kinetic delays typically associated with the assembly of large inflammasome platforms (57). Furthermore, caspase-11-mediated potassium efflux can secondarily trigger the NLRP3 inflammasome, creating a potent, self-reinforcing feed-forward loop that accelerates the collapse of the alveolar-capillary barrier (58).

Table I. Pyroptosis during S-ALI.

Species	Inducer	Tissue/cell	Time/stage	Pyroptosis assessments	(Refs.)
Mice	PBS-Exo or TNF-Exo	Lung tissues	3 h	Elevated levels of pyroptosis markers NLRP3, caspase-1 and GSDMD	(75)
Mice	CLP	Lung tissues	24 h	The expression of NLRP3 and GSDMD cleavage	(130)
Mice	LPS	Lung tissues	8 h	The expression of NLRP3, Caspase 1, Caspase 11, GSDMD, IL-1β, IL-18, TGF-β, CD86, CD206, iNOS, and Arg-1	(75)
Mice	LPS	Lung tissues	24 h	Assess the protein expression of P45,P20, CASP1,s P53, GSDMD, GSDME, and AIM2	(159)
Mice	CLP	Lung tissues	24 h	The expression of NLRP3, ASC, AIM2, IL-1β and caspase-1	(160)
Mice	LPS	Lung tissues	24 h	The expression of NLRP3	(161)
Mice	LPS	Lung tissues	24 h	The expression of NLRP3, GSDMD, caspase-1	(162)
Mice	LPS	Human alveolar epithelial cell line	24 h	The expression of NLRP3, caspase-1, caspase 1, p20 GSDMD, GSDMD-NT and CRAMP	(82)
Mice	LPS	Lung tissues	12 h	The expression of NLRP3, IL-1β, IL-18 and Cle-GSDMD	(163)
Humans	Sepsis (ICU patients)	Plasma microparticles	Within 24 h of ICU admission	Detection of active GSDMD (p30) in circulating microparticles; elevated in septic patients compared with non-septic ICU controls; associated with monocyte-derived vesicles	(121)
Humans	Sepsis with or without ARDS	Serum	At diagnosis	Increased serum NLRP3 levels in sepsis-associated ARDS compared with sepsis alone; correlated with APACHE II, SOFA scores, and 28-day mortality	(21)
Humans	Severe respiratory infection (COVID-19)	Serum	On admission	Elevated serum GSDMD levels associated with disease severity, need for mechanical ventilation, and poor clinical outcomes	(164)
Humans	Acute lung injury/ARDS	Serum	During hospital ization	Increased circulating cleaved GSDMD (N-GSDMD), IL-1β, and IL-18 levels; correlated with lung injury severity	(165)

S-ALI, sepsis-induced acute lung injury; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; PBS-Exo, phosphate-buffered saline-derived exosomes; TNF-Exo, tumor necrosis factor-stimulated exosomes; ECs, endothelial cells; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; AIM2, absent in melanoma 2; GSDMD, gasdermin D; GSDME, gasdermin E; NT-GSDMD, N-terminal gasdermin D; caspase-1, cysteine-aspartic protease-1; caspase-11, cysteine-aspartic protease-11; IL, interleukin; TGF-β, transforming growth factor-β; iNOS, inducible nitric oxide synthase; Arg-1, arginase-1; CRAMP, cathelicidin-related antimicrobial peptide; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

From a precision medicine perspective, recognizing the dominance of this LPS-caspase axis is essential, as it identifies a subset of patients who remain refractory to NLRP3-specific inhibition, but may demonstrate clinical responsiveness to strategies targeting noncanonical executioners.

Apoptotic caspase-mediated pyroptosis pathway. The molecular plasticity between silent apoptosis and explosive pyroptosis is governed by the strategic recruitment of apoptotic caspases to the gasdermin execution machinery. As illustrated in Fig. 4C, various stimuli including influenza A virus, tumor necrosis factor-α (TNF-α), death receptors, reactive oxygen species and chemotherapeutic drugs can trigger this pathway (59-62). These stimuli activate the extrinsic apoptotic pathway through death receptors, leading to the recruitment of adaptor proteins, such as FADD and RIPK1, which activate pro-caspase-8 into active caspase-8. Simultaneously, the intrinsic (mitochondrial) pathway is engaged via cytochrome *c* release from the mitochondria, resulting in the activation of caspase-9. Both initiator caspases (caspase-8 and caspase-9) then converge to activate the executioner caspases, primarily caspase-3, as well as caspase-6 and caspase-7. These executioner caspases cleave gasdermin family proteins, including gasdermin B (GSDMB), gasdermin C, GSDMD

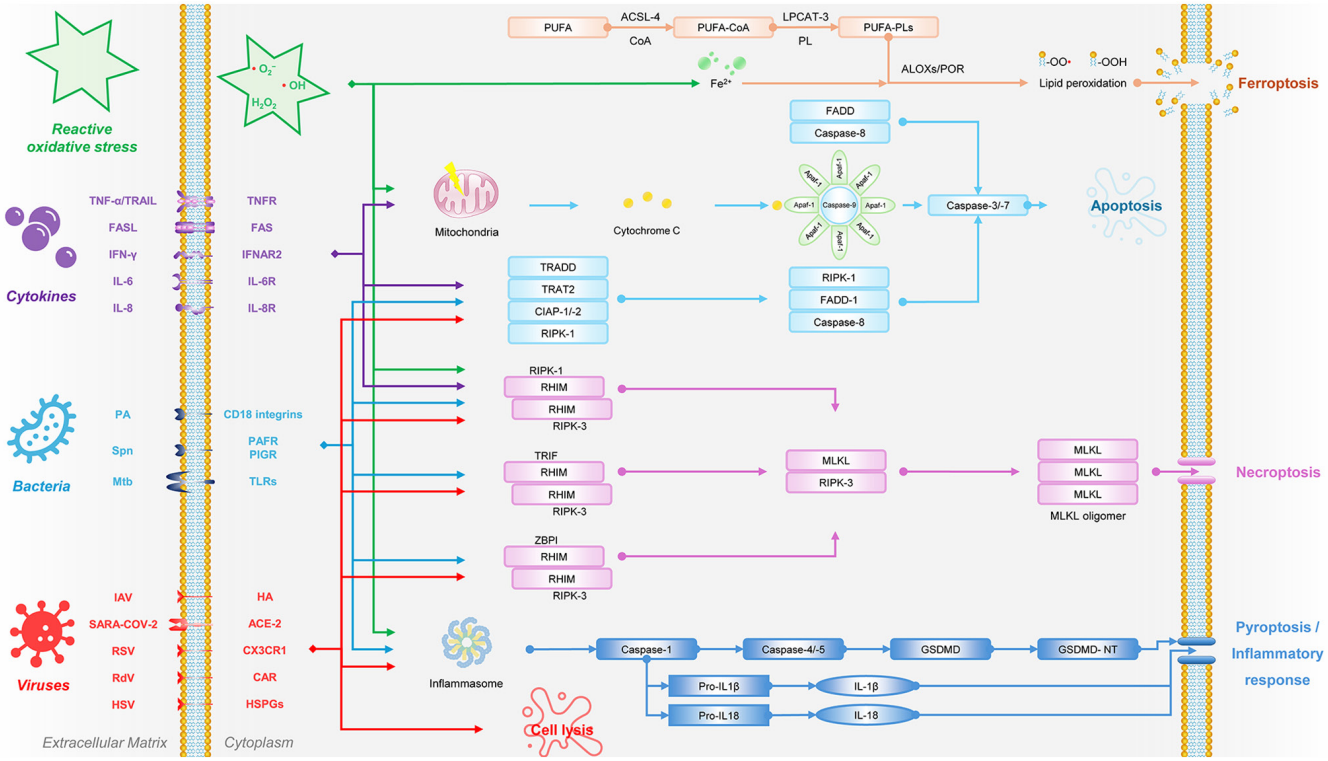

Figure 3. Schematic illustration of multiple cell death mechanisms in sepsis-induced acute lung injury. In sepsis-induced acute lung injury, excessive levels of reactive oxygen species together with abundant pro-inflammatory cytokines (TNF-α/TRAIL, FAS-L, IFNs, IL-6, IL-8), bacterial components and viral PAMPs activate multiple signaling pathways through their cognate receptors on the plasma membrane. These stimuli converge on four major programmed cell death modalities that contribute to alveolar epithelial and endothelial damage. In the ferroptosis pathway, ACSL4 and LPCAT3 mediate the incorporation of PUFAs into membrane phospholipids, followed by iron-dependent lipid peroxidation catalyzed by ALOXs/POR, leading to lethal lipid ROS accumulation and membrane disruption. In the apoptosis pathway, death receptor signaling recruits FADD and activates caspase-8, while mitochondrial cytochrome *c* release forms the apoptosome, resulting in the activation of executioner caspase-3/7. When caspase-8 activity is inhibited, the necroptosis pathway is triggered via RIPK1-RIPK3-mediated phosphorylation and oligomerization of MLKL, causing plasma membrane rupture. Simultaneously, inflammasome activation drives caspase-1 (and caspase-4/5) to cleave pro-IL-1β and pro-IL-18 into mature forms and process GSDMD into the pore-forming GSDMD-NT fragment, executing pyroptosis with cell lysis and massive release of pro-inflammatory cytokines. Mitochondria, RIPK1/RIPK3, and caspases serve as central molecular switches that integrate these danger signals and dictate the predominant mode of cell death, ultimately exacerbating lung inflammation, barrier dysfunction, and tissue injury in sepsis-induced acute lung injury. The figure was generated using BioGDP.com (BioGDP Scientific Illustration Platform, https://BioGDP.com). PAMPs, pathogen-associated molecular patterns; PUFAs, polyunsaturated fatty acids; PUFA-PLs, polyunsaturated fatty acid-containing phospholipids); ALOXs/POR, arachidonate lipoxygenases/cytochrome P450 oxidoreductase; ROS, reactive oxygen species; FADD, Fas-associated protein with death domain; GSDMD, gasdermin D; GSDMD-NT, gasdermin D N-terminal domain; RIPK, receptor-interacting protein kinase.

and gasdermin E (GSDME), to generate their pore-forming N-terminal fragments (23,60).

Caspase-3, traditionally viewed as a terminal executioner of non-inflammatory apoptosis, can cleave GSDME to generate GSDME-N fragments, which effectively switches the mode of cell death to pro-inflammatory pyroptosis. The clinical trajectory of S-ALI is profoundly influenced by the tissue-specific expression profiles of GSDME, as high baseline expression in pulmonary epithelial cells converts otherwise resolving apoptotic signals into localized tissue lysis and inflammatory amplification (63-65). Similarly, caspase-8 functions as a molecular rheostat under conditions of TNF-α stimulation or pathogenic stress, bridging these death pathways via the direct cleavage of GSDMD in specific immune cell subsets (66). This molecular crosstalk provides a profound stratification marker for clinicians in the ICU; evaluating the GSDME signature in pulmonary cells predicts whether a patient will exhibit a hyper-inflammatory phenotype or a more favorable resolving death phenotype (66).

Granzyme-mediated pathway. Beyond endogenous cell-autonomous signaling, the granzyme-mediated pathway highlights the critical role of external immune executioners in driving irreversible pulmonary tissue lysis. Perforin-delivered granzymes (particularly GZMA and GZMB) from over-activated cytotoxic T-lymphocytes or natural killer cells can directly cleave gasdermin family members, such as GSDMB or GSDME, in an action that is entirely independent of conventional caspase activity (67-72) (Fig. 4D). In the hyper-active immune phase often observed in early sepsis, this pathway represents a significant mechanism of collateral damage where the adaptive immune system of the exacerbates alveolar wall destruction and tissue dysfunction. Identifying this lymphocyte-driven lysis shifts the focus of personalized therapy toward immunomodulatory stratification, particularly for those critically ill patients who exhibit abnormally high cytotoxic activity in bronchoalveolar lavage fluid, effectively moving the field beyond the traditional constraints of innate immune-centric treatment models (73).

3. Cellular orchestration of pyroptosis in S-ALI

The pathological progression of S-ALI is dictated by the coordinated execution of cell death across distinct

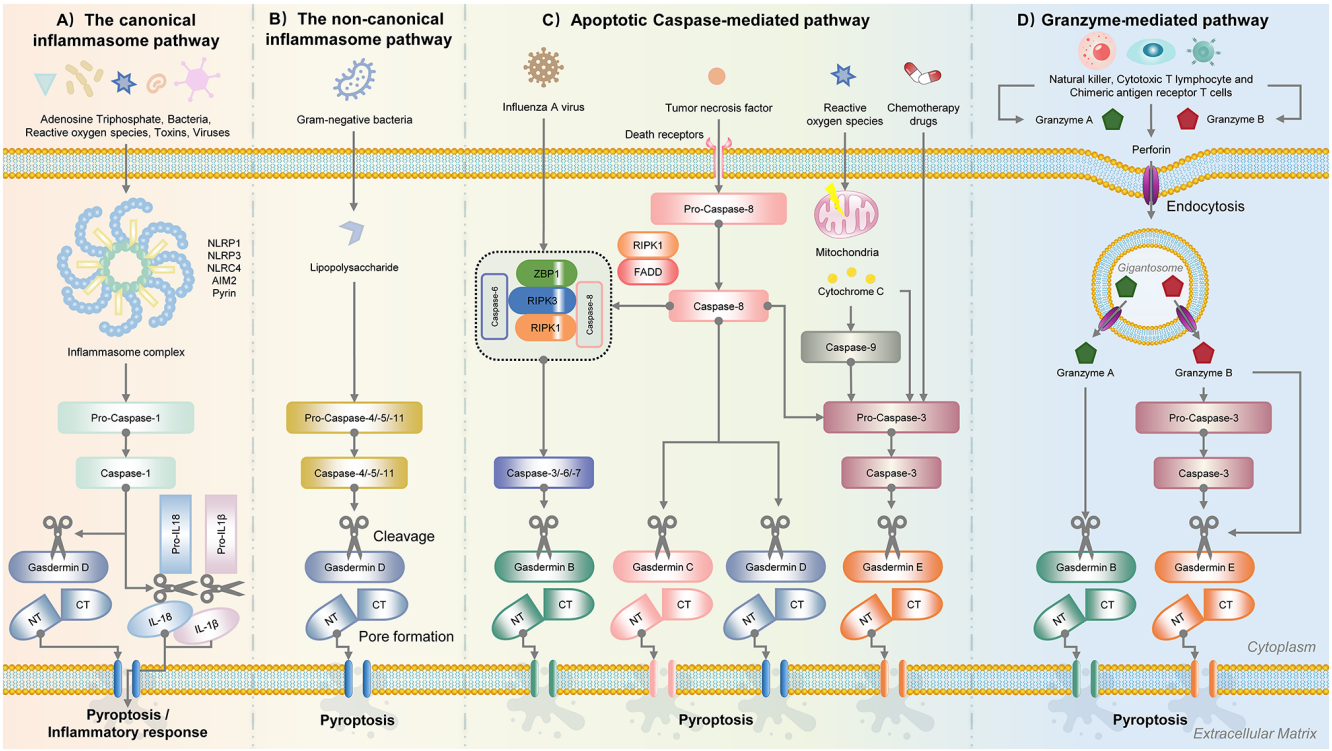

Figure 4. Pyroptosis is a lytic, pro-inflammatory form of programmed cell death executed primarily by gasdermin family proteins. The schematic diagram illustrates four major molecular pathways leading to pyroptosis: (A) The canonical inflammasome pathway: Pathogen-associated molecular patterns and damage-associated molecular patterns, such as adenosine triphosphate, bacteria, reactive oxygen species, toxins, and viruses, trigger the assembly of inflammasome complexes containing NLRP1, NLRP3, NLRC4, AIM2, or Pyrin. The inflammasomes recruit and activate pro-caspase-1 into active caspase-1, which cleaves GSDMD to generate the N-terminal fragment (NT). GSDMD-NT oligomerizes and forms pores in the plasma membrane, resulting in cell swelling, rupture and the release of mature pro-inflammatory cytokines (IL-1β and IL-18). (B) The non-canonical inflammasome pathway: Gram-negative bacterial lipopolysaccharide directly activates caspase-4/5 (human) or caspase-11 (mouse), which cleave GSDMD to produce the pore-forming N-terminal fragment, inducing pyroptosis independent of canonical inflammasome activation. (C) Apoptotic caspase-mediated pathway: Various stimuli including influenza A virus, tumor necrosis factor, death receptors, reactive oxygen species and chemotherapeutic drugs activate the extrinsic (caspase-8 via FADD and RIPK1) or intrinsic (mitochondrial cytochrome *c* release, leading to caspase-9) apoptotic pathways. These initiator caspases activate executioner caspases (caspase-3/6/7), which can cleave gasdermin B, C, D, or E, thereby converting apoptotic signals into pyroptotic outcomes through pore formation. (D) Granzyme-mediated pathway: Cytotoxic T-lymphocytes and natural killer cells release granzyme A and granzyme B via perforin-mediated endocytosis. Granzyme B activates caspase-3, while both granzymes can directly cleave gasdermin B or E, leading to membrane pore formation and pyroptosis. In all pathways, the formation of gasdermin pores in the plasma membrane causes characteristic pyroptotic cell lysis, release of intracellular contents, and amplification of inflammatory responses. The figure highlights the diversity and crosstalk of pyroptotic signaling, which plays critical roles in host defense against infection, as well as in the pathogenesis of inflammatory and infectious diseases. The figure was generated using BioGDP.com (BioGDP Scientific Illustration Platform, https://BioGDP.com). NLRP, nucleotide-binding oligomerization domain-like receptor protein; GSDMD, gasdermin D; GSDMD-NT, gasdermin D N-terminal domain; RIPK, receptor-interacting protein kinase.

pulmonary compartments, creating a spatio-temporal map of organ failure (74). Instead of a generic 'final common pathway', the cell-specific activation of pyroptotic machinery dictates the biophysical transition from localized infection to systemic respiratory collapse. Understanding these cellular roles provides the necessary mechanistic depth to define patient-specific clinical endotypes and to develop precision-guided ICU interventions (75).

Alveolar macrophages: The primary inflammatory detonator. Alveolar macrophages function as the frontline sensors of the pulmonary microenvironment. In the initial phase of S-ALI, macrophage pyroptosis functions as a high-potency 'molecular detonator' that amplifies pathogen-driven signals into an expansive cytokine storm (76). The activation of the NLRP3 inflammasome facilitates the rapid, unconventional secretion of IL-1β and high mobility group box 1, which orchestrate neutrophil recruitment and prime the lung parenchyma for secondary damage (77). This macrophage-centric execution accounts for the systemic hyper-inflammation observed in 'hyper-inflammatory' subphenotypes (78). The intensity of this detonator phase suggests that early-window targeting of macrophage-specific gasdermin activation could preemptively halt the inflammatory cascade before irreversible structural destruction occurs.

Endothelial cells: The driver of microvascular permeability. The structural integrity of the alveolar-capillary barrier is fundamentally dependent on the semi-permeable microvascular endothelium. In the evolution of S-ALI, endothelial pyroptosis serves as the primary driver for the catastrophic loss of vascular barrier function, leading to the hallmark accumulation of protein-rich edema (26). The intracellular sensing of LPS triggers non-canonical signaling through caspase-11, which executes endothelial lysis via GSDMD-mediated pore formation (79). This cell-specific destruction explains the clinical transition to profound hypoxemia, as endothelial pore formation represents a decisive biophysical transition

point (80). Furthermore, the release of pro-thrombotic factors following membrane rupture exacerbates microcirculatory dysfunction, linking pyroptosis to the coagulation abnormalities frequently observed in patients with sepsis (81).

Epithelial cells: The executioner of gas exchange failure. While endothelial damage drives leakage, the pyroptosis of alveolar epithelial cells (AECs), particularly type II cells, dictates the failure of respiratory mechanics. The depletion of AECII through pyroptotic pathways directly impairs pulmonary surfactant production, contributing to alveolar collapse and refractory atelectasis (82). Unlike apoptosis, this regulated lysis prevents effective lung repair and potentially initiates pathways driving late-stage fibroproliferation (83). Recognizing the epithelial compartment as a terminal executioner provides a translational rationale for strategies that specifically preserve AEC integrity. Such protection is essential for maintaining mechanical stability in patients undergoing invasive mechanical ventilation, where epithelial loss increases the risk of ventilator-induced lung injury (84).

Cellular crosstalk and the PANoptosome complex. Critical to the exacerbation of S-ALI is the molecular crosstalk between these cellular compartments, often converging on the assembly of the PANoptosome (85,86). This integrated death mode involves the coordinated activation of pyroptosis, apoptosis and necroptosis, allowing the cell to bypass individual signaling bottlenecks (87). The discovery of PANoptosis explains the 'therapeutic escape' observed in clinical trials, where inhibiting a single protease fails due to the compensatory activation of parallel death modes (83). For instance, selective caspase-1 inhibitors (such as VX-765) in inflammatory lung injury models and related acute respiratory distress syndrome (ARDS) trials have exhibited limited sustained efficacy, as the blockade of pyroptosis leads to the compensatory activation of apoptosis and necroptosis pathways via caspase-8 and RIPK3/MLKL, resulting in persistent tissue damage and cytokine release (88). Similarly, attempts at single caspase-8 inhibition in sepsis-associated contexts have demonstrated incomplete protection due to upregulation of alternative PANoptosome components (89). Integrating PANoptosome dynamics into the S-ALI framework underscores the necessity for 'combination precision medicine' that addresses these convergent molecular hubs to effectively mitigate multifaceted tissue destruction (90).

4. Precision therapeutic landscape for pyroptosis in S-ALI

Pyroptosis, a pro-inflammatory programmed cell death mediated by the gasdermin family, is defined as a distinct inflammatory phenotype in S-ALI, with a pathological trajectory that contributes to irreversible alveolar damage (91). From a precision medicine perspective, pyroptosis serves as both a mechanistic driver and a stratification-relevant therapeutic target. Lineage plasticity, a fundamental property that enables cells to shift between different functional states, has attracted increased interest in recent years in the context of sepsis-associated acute lung injury. Intratumoral-like heterogeneity partly reflects the lineage plasticity of lung cells during S-ALI progression. Distinct clusters of dying cells co-exist in both canonical and non-canonical pyroptosis pathways compared to traditional single-mode death models. These clusters differ significantly in marker genes, molecular signaling pathways, differentiation states and transcriptional profiles, indicating a marked increase in transcriptional heterogeneity during the progression if S-ALI. The intermediate and transitional state of pyroptotic injury is evident, as multiple pathways exhibit consistent shifts along the histological transition from early inflammation to terminal lysis, consistent with previous bulk sequencing data (90). This dynamic transition provides a biological foundation for stage-dependent and biomarker-guided therapeutic intervention. An epithelial-endothelial cluster shared among injury subtypes demonstrates potent differentiation potential according to the transcriptional differentiation trajectory. Gene expression, pathway enrichment and clinical biomarker data point to the stem-like characteristic of this subpopulation, suggesting it as the potentially pioneering force of lineage plasticity for the progression of S-ALI. Previous rseearch tracing histological transformation in septic lungs have identified an undifferentiated, stem-like state that emerges during the transition, with cells exhibiting basal-like features and the activation of NF-κB and complement signaling pathways (92). Key regulatory nodes exhibit basal origins with marked upregulation of NLRP3 and complement component 5a (C5a) receptor (C5aR) signaling pathways (92). The expression of the associated gene module gradually increases along the histological transition in experimental models. Significant discordance exists between preclinical success and clinical reality. This discordance may be partially attributed to the lack of patient stratification (2). In this context, linking biomarker-defined endotypes with pathway-specific interventions forms the core of a precision roadmap. The hyperinflammatory or pyroptosis-high endotype, characterized by elevated plasma GSDMD fragments and IL-18, is associated with activation of canonical or noncanonical inflammasome pathways and may be matched with corresponding targeted therapies, with the potential to improve clinically relevant outcomes such as ventilator-free days and organ failure scores. Current therapeutic strategies mainly focus on a single pathway, but underestimate the high plasticity of septic cells. Therefore, a shift toward biomarker-guided, stage-specific intervention is required to overcome treatment resistance and improve therapeutic precision. Further studies are warranted to elucidate the precise role of stem-like cells in S-ALI progression and to assess their potential therapeutic implications.

Molecular decoupling and strategic targeting of the canonical NLRP3 axis. The canonical NLRP3-caspase-1 axis serves as a primary molecular detonator in S-ALI, with the intensity of its activation being closely associated with alveolar-capillary barrier disruption (93). Distinct regulatory clusters are governed by endogenous rheostats, such as heat shock factor 1 and heat shock protein 8, which modulate NLRP3 ubiquitination to prevent the irreversible formation of the ASC speck complex (94,95).

These regulatory clusters differ significantly in molecular signaling pathways and differentiation states, indicating a dramatic increase in transcriptional heterogeneity during sepsis progression. The intermediate and transitional state of

NLRP3 priming is evident, as multiple genes and pathways show consistent shifts from early priming to terminal execution. A priming cluster shared across models demonstrates potent differentiation potential according to the transcriptional differentiation trajectory. Pathway enrichment points to the stem-like characteristic of this subpopulation, suggesting it as the potentially pioneering force of lineage plasticity for canonical pyroptosis. A vast repertoire of pharmacological agents has demonstrated robust efficacy in preclinical models (96-122); however, the discordance between murine success and clinical reality underscores the challenge of target engagement in the human septic niche. For example, colchicine suppresses NLRP3 inflammasome assembly and oxidative stress in LPS-induced ALI (123), while metformin inhibits GSDMD activation and downstream inflammatory amplification in CLP models (96), both demonstrating consistent attenuation of pyroptosis-associated lung injury *in vivo*. A critical barrier in translating pyroptosis-targeted strategies from murine models to human sepsis lies in species-specific divergence in inflammasome signaling, particularly the absence of direct orthology between murine caspase-11 and human caspase-4/5, which exhibit distinct activation thresholds and ligand sensitivities to cytosolic LPS (53). This molecular non-equivalence complicates the extrapolation of caspase-11-centered findings from LPS- or CLP-induced murine models of SALI to human patients in the ICU, where caspase-4/5-driven noncanonical inflammasome activation may follow different kinetics and cellular distribution (55).

Several therapies with potential applicability in the ICU setting have been described. These include anakinra (IL-1 receptor antagonist), which is already used in critically ill patients and has favorable pharmacologic feasibility due to its subcutaneous or intravenous administration, relatively predictable pharmacokinetics even in organ dysfunction, and established safety profile in sepsis trials (3). Mesenchymal stromal cells (MSCs) have also been administered intravenously in multiple ARDS ICU trials, although their feasibility is limited by the need for cell preparation and variable engraftment (124). By contrast, direct NLRP3 inhibitors (e.g., DFV890) and GSDMD inhibitors remain largely investigational, with limited data on ICU pharmacokinetics, potential drug interactions and tissue penetration in critically ill patients with altered hemodynamics and pulmonary vascular injury (125).

In addition, pharmacokinetic and pharmacodynamic constraints in critically ill patients, including altered drug absorption, organ dysfunction and unpredictable tissue distribution within injured pulmonary microvasculature, further limit reliable target engagement despite robust preclinical efficacy signals (126).

The expression of NLRP3-associated gene modules gradually increases along the histological transition in experimental models, while clinical translation remains limited by the lack of patient stratification (127,128). Clinical applicability of this axis depends on the early identification of patients with high inflammasome activity through plasma GSDMD cleavage products and IL-18 levels, preferably within 24-48 h of admission to the ICU. Emerging clinical signals from NLRP3 inhibitors, such as DFV890 and the soluble urokinase plasminogen activator receptor (suPAR)-guided administration of anakinra suggest that identifying hyper-pyroptotic endotypes is the only viable path to translating these findings into survival benefits (125,129). Therapeutic efficacy is likely to be maximized during the early hyperinflammatory phase, whereas late-stage administration risks exacerbating immunosuppression. The full pharmacological landscape of inhibitors targeting the canonical NLRP3-caspase-1-GSDMD axis is synthesized in Table II. Table II provides a comprehensive summary of various pharmacological agents targeting different nodes (priming, assembly and execution) of the canonical inflammasome pathway. It lists specific agents (e.g., MCC950, metformin, colchicine and natural compounds), their experimental inducers (mainly LPS or CLP), molecular mechanisms, and key outcomes in murine models, such as reduced pulmonary damage, reduced pyroptosis, reduced NLRP3 activation, reduced GSDMD cleavage, and improved survival, along with associated risks and limitations.

Targeting the canonical NLRP3 inflammasome pathway has shown promising results in preclinical studies (Table II).

Non-canonical signaling as a biophysical driver of endothelial plasticity. Lineage plasticity is particularly evident in the non-canonical caspase-4/5/11 pathway (86). Unlike the canonical axis, this pathway directly senses cytosolic LPS within pulmonary endothelium, triggering rapid GSDMD-mediated membrane permeabilization (130). Distinct clusters of endothelial cells co-exist in both acute and subacute phases of lung injury compared to myeloid-dominant canonical models. These clusters differ significantly in marker genes, molecular signaling pathways and differentiation states, indicating a marked increase in transcriptional heterogeneity during endothelial transformation. The intermediate and transitional state of non-canonical activation is evident, as multiple pathways show consistent shifts along the histological transition from localized inflammation to systemic alveolar flooding (4). An upstream humoral-cellular crosstalk cluster shared among different sepsis models demonstrates potent differentiation potential according to the transcriptional differentiation trajectory. Pathway enrichment points to the stem-like characteristic of this subpopulation, suggesting it as the potentially pioneering force of lineage plasticity for non-canonical pyroptosis. The complement component 3a/C5a-C5aR axis serves as a key modulator, while vilobelimab has shown clinical success in severe respiratory failure (4). Notably, vilobelimab-mediated C5a blockade represents a clinically translatable example of complement-targeted intervention that has progressed beyond preclinical validation into randomized human ARDS trials, highlighting a partial bridge between murine non-canonical inflammasome models and ICU feasibility (131). The significant activation of non-canonical clusters occurs across disease phases. Current therapeutic strategies for this axis remain limited and require careful temporal control to avoid compromising host defense mechanisms in the early phase of sepsis. Targeting intratumoral heterogeneity or stem-like endothelial nodes has been proposed as a novel strategy to overcome treatment resistance. The full list of inhibitors targeting the non-canonical inflammasome pathway is synthesized in Table III. Table III summarizes therapeutic strategies targeting the non-canonical (caspase-4/5/11) pathway in S-ALI, including upstream complement modulation, caspase-11 inhibition and

Table II. Inhibition of the canonical inflammasome pathway of pyroptosis for the treatment of S-ALI.

Targeting node	Agents	Inducer	Molecular mechanism	Orchestration evidence level	Key outcomes or risks/limitations	(Refs.)
Priming/ assembly	Buformin	LPS	Inhibited NLRP3-mediated pyroptosis	Murine: Reduced pulmonary damage, reduced cytokines, reduced pyroptotic signaling.	Metabolic effects; limited human data	(161)
Priming	HSF1	CLP	Represses NLRP3 via NF-κB inhibition; promotes NLRP3 ubiquitination and inhibits caspase-1/IL-1β	Murine CLP: HSF1 deficiency worsens injury, overexpression improves survival	Gene-level modulation; translational feasibility issues	(94)
Priming	HSPA8 (Hsc70/HSP70)	CLP	Inhibits NLRP3 ubiquitination	Murine: Reduced pyroptosis, improved survival.	Chaperone modulation challenges	(95)
Assembly	Peptidyl arginine deiminases (PADI2/4)	PA pneumonia-induced sepsis	Inhibited expression of NLRP3 inflammasomes	Murine: Reduced NLRP3 formation, ameliorated lung injury.	Enzyme deletion approach; limited pharmacological data	(166)
Assembly	Colchicine	LPS	Inhibits NLRP3 inflammasome formation and oxidative stress	Murine: Reduced pyroptosis in alveolar macrophages.	Gastrointestinal toxicity	(123)
Assembly	6-Gingerol	LPS	Decreases NLRP3, ASC, caspase-1; activates Nrf2/HO-1	Murine: Reduced inflammatory infiltration, reduced peribronchial thickening.	Limited human PK data	(167)
Priming/ execution	Metformin	CLP	Suppresses GSDMD activation and up-regulation of S100A8/A9, NLRP3, ASC	Murine: Reduced sepsis-induced GSDMD activation.	Metabolic effects	(96)
Priming	*Commelina communis* L.	LPS	Suppresses NF-κB/NLRP3 via metabolic and gut microbiota modulation	Murine: Reduced NLRP3 signaling	Herbal standardization issues	(97)
Assembly	4-Benzene-indol derivative	LPS	Disrupts NLRP3-NEK7 interaction and inflammasome assembly	Murine: Reduced NLRP3 activation	Early preclinical stage	(98)
Priming	Xuebijing injection	CLP	Downregulates c-Jun and inhibits NLRP3 activation	Murine: Reduced NLRP3 inflammasome	Complex herbal mixture; standardization challenges	(99)
Execution	Phillyrin	LPS	Downregulates NLRP3-caspase-1-GSDMD pathway	Murine: Reduced pyroptosis signaling	Limited human data	(100)
Assembly	Tangeretin	LPS	Inhibits ROS-mediated NLRP3 via PLK1/ AMPK/DRP1 axis	Murine: Reduced NLRP3 activation	Bioavailability issues	(162)
Priming	Mangiferin	LPS	Inhibits NLRP3 in NF-κB-dependent manner in macrophages	Murine: Reduced NLRP3 activation	Limited clinical translation	(101)
Execution	Dihydro-myricetin	CLP	Inhibits NLRP3 inflammasome pathway (NLRP3, ASC, caspase-1, GSDMD, IL-1β/IL-18)	Murine: Reduced inflammasome components	Herbal standardization	(104)
Caspase-1	Anisodamine hydrobromide	*In vitro*: LPS; *In vivo*: CLP	Downregulates NLRP3, caspase-1, GSDMD, IL-1β/IL-18; similar to AC-YVAD-CMK	Murine + cell: Reduced pyroptosis	Anticholinergic side effects	(105)

Table II. Continued.

Targeting node	Agents	Inducer	Molecular mechanism	Orchestration evidence level	Key outcomes or risks/limitations	(Refs.)
Priming	Chlorogenic acid	LPS	Downregulates ROS/TXNIP/NLRP3 pathway	Murine: Reduced inflammatory molecules and pyroptosis	Limited human data	(106)
Caspase-1	Loganin	*In vitro*: LPS; *In vivo*: CLP	Inhibits NLRP3-mediated caspase-1 activation and IL-1β secretion	Murine + cell: Reduced IL-1β	Limited clinical experience	(107)
Priming	Andrographolide	*In vitro*: LPS; *In vivo*: CLP	Inhibits NLRP3 via RAGE/PI3K/AKT/mTOR pathway	Murine + cell: Reduced NLRP3 activation	Bioavailability issues	(108)
Priming	Yam glycoprotein	LPS	Activates NLRP3 and TLR4/NF-κB signaling (inhibitory effect observed)	Murine: Modulation of inflammasome	Complex natural product	(110)
Assembly/priming	Oridonin	LPS	Inhibits NLRP3 inflammasome and NF-κB pathway	Murine: Reduced pro-inflammatory pathways	Limited human data	(111)
Execution	Alpha-linolenic acid	LPS	Inhibits Pyrin inflammasome and reduces NETs, pyroptosis proteins	Murine: Reduced Cl-caspase-1, Cl-GSDMD, and IL-1β	Nutritional compound; dose optimization needed	(113)
Execution	Emodin	LPS	Regulates NLRP3 inflammasome-dependent pyroptosis pathway	Murine: Reduced pyroptosis signaling	Potential toxicity	(116)
Assembly	Honokiol	LPS	Reduces oxidative stress and inhibits NLRP3-mediated pyroptosis	Murine: Reduced oxidative stress and pyroptosis	Limited clinical data	(119)
Priming	Erythropoietin	LPS	Suppresses NLRP3 via EPOR/JAK2/STAT3 and NF-κB inhibition	Murine: Reduced NLRP3 activation	Hematological effects	(120)

S-ALI, sepsis-induced acute lung injury; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDMD, gasdermin D; IL, interleukin; HSF1, heat shock factor 1; HSC70, heat shock cognate protein 70; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; PA, Pseudomonas aeruginosa; PADI2/4, peptidyl arginine deiminases 2/4; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; PK, pharmacokinetics; S100A8/A9, S100 calcium-binding protein A8/A9; NEK7, NIMA-related kinase 7; ROS, reactive oxygen species; PLK1, polo-like kinase 1; AMPK, AMP-activated protein kinase; DRP1, dynamin-related protein 1; TXNIP, thioredoxin-interacting protein; RAGE, receptor for advanced glycation end products; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; TLR4, Toll-like receptor 4; NETs, neutrophil extracellular traps; Cl-caspase-1, cleaved caspase-1; Cl-GSDMD, cleaved gasdermin D; EPOR, erythropoietin receptor; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; AC-YVAD-CMK, caspase-1 inhibitor acetyl-Tyr-Val-Ala-Asp-chloromethylketone.

Table III. Inhibition of the non-canonical inflammasome pathway of pyroptosis for the treatment of S-ALI.

Targeting strategy	Representative agents	Inducer	Molecular mechanism and orchestration	Evidence level and key outcomes	Risks/limitations	(Refs.)
Upstream complement	C3a-C3aR axis	CLP	Blocks NLRP3/caspase-1 and caspase-11 pathways	Murine: Reduced endothelial pyroptosis and vascular leakage	Complement suppression may impair host defense	(4)
Caspase-11	Heparin	CLP	Inhibits caspase-11 signaling	Murine: Reduced lung injury	Anticoagulant-related bleeding risk	(168)
Caspase-11	W-54011	LPS	Inhibits expression of caspase-11	Murine: Reduced caspase-11 expression	Limited data	(169)
Upstream complement	Vilobelimab (IFX-1, anti-C5a)	Severe sepsis/ COVID-19 ARDS	Selective C5a blockade; PK/PD suppression of C5a	Human: Reduced 28-day mortality in COVID-19 ARDS; safe in Phase 2 sepsis	Infection risk; stronger in COVID-19 ARDS	(131)
Regulatory	pIgR antibody	LPS	Reduces pro-caspase-11, caspase-11 and GSDMD activation	Murine: Reduced lung injury, improved survival	Antibody delivery challenges	(170)
Macrophage polarization	Dexmedetomidine	CLP/LPS-stimulated RAW264.7	Promotes M2 polarization; inhibits RAGE/Caspase-11 pathway	Murine + cell: Reduced pyroptosis	Sedative effects	(171)
Caspase-11	Luteolin	CLP	Inhibits caspase-11, caspase-1, GSDMD, IL-1α/IL-1β	Murine: Reduced pyroptosis	Limited human data	(172)
Caspase-11	Lianhua Qingke (LHQK)	LPS	Suppresses caspase-11/ caspase-1 cleavage and GSDMD pore formation	Murine: Reduced IL-1β maturation	Herbal standardization	(173)
Transcriptional regulation	Bhlhe40	LPS	Represses canonical and non-canonical signaling	Murine + *in vitro*: Reduced GSDMD-mediated pyroptosis and ALI	Transcription factor targeting difficulty	(174)
Caspase-11	Carbon monoxide	LPS	Reduces cleaved caspase-11, N-GSDMD, IL-1β/IL-18; increases NRF-2	*In vitro*: Reduced pyroptosis	Delivery and toxicity concerns	(175)
Caspase-11	Glycyrrhizin	CLP	Inhibition of HMGB1 reduces caspase-11-dependent pyroptosis	Murine: Reduced pyroptosis	Limited clinical translation	(176)
Caspase-11	Abscisic acid (ABA)	LPS	Inhibits membrane pores, GSDMD cleavage, caspase-11/1 activation	Murine + *in vitro*: Reduced pyroptosis	Limited human data	(177)
Canonical + non-canonical	Isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate	LPS	Reduces active-caspase-1, NLRP3, ASC, GSDMD, caspase-4	Murine: Reduced pyroptosis pathways	Early preclinical	(178)

Table III. Continued.

Targeting strategy	Representative agents	Inducer	Molecular mechanism and orchestration	Evidence level and key outcomes	Risks/limitations	(Refs.)
Cellular therapy	hUC-MSCs	CLP	Inhibits TLR4/caspase-11/GSDMD signaling	Murine: Reduced pyroptosis	Cell therapy heterogeneity	(179)
Caspase-11	MANF	LPS	Inhibits caspase-11 and GSDMD activation	Murine: Reduced caspase-11 and GSDMD-N	Protein-based delivery issues	(180)

S-ALI, sepsis-induced acute lung injury; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; C3a, complement component 3a; C3aR, complement component 3a receptor; C5a, complement component 5a; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDMD, gasdermin D; IL, interleukin; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; caspase-1, cysteine-aspartic protease-1; caspase-11, cysteine-aspartic protease-11; caspase-4, cysteine-aspartic protease-4; HMGB1, high mobility group box 1; RAGE, receptor for advanced glycation end products; TLR4, Toll-like receptor 4; RAW264.7, murine macrophage cell line; hUC-MSCs, human umbilical cord-derived mesenchymal stromal cells; Bhlhe40, basic helix-loop-helix family member e40; MANF, mesencephalic astrocyte-derived neurotrophic factor; NRF2, nuclear factor erythroid 2-related factor 2; PK/PD, pharmacokinetics/pharmacodynamics; ALI, acute lung injury.

cellular therapies. Table III lists representative agents, molecular mechanisms, key outcomes (such as reduced endothelial pyroptosis, reduced vascular leakage, reduced lung injury and improved survival), as well as risks and limitations for each approach.

PANoptosome orchestration and the paradigm of death-mode switching. The concept of lineage plasticity in the septic lung is further reflected in the integrated PANoptosome complex, which enables a distinct phenotype of cell death with potential for state-shifting (87). Distinct clusters of dying cells where pyroptosis co-exists with apoptosis and necroptosis are more evident compared to traditional single-mode death models (90). These clusters differ significantly in marker genes, molecular signaling pathways and differentiation states, indicating a dramatic increase in transcriptional heterogeneity during death-mode switching. The intermediate and transitional state of GSDME-mediated injury is evident, as multiple pathways show consistent shifts from early apoptosis to terminal lysis (83). An epithelial cluster shared across injury groups demonstrates potent differentiation potential according to the transcriptional differentiation trajectory. Gene expression and pathway enrichment point to the stem-like characteristic of this subpopulation, suggesting it as the potentially pioneering force of lineage plasticity for PANoptosis in S-ALI. Caspase-3 and caspase-8 function as critical hubs for death-mode switching (132). For instance, ligustrazine suppresses both caspase-8 and NLRP3-caspase-1 signaling simultaneously, illustrating a multi-node regulatory strategy capable of modulating pyroptosis-apoptosis crosstalk within PANoptotic networks in septic lung injury (133). The significant activation of compensatory pathways occurs when one executioner is inhibited (134). This coordinated activation highlights the limitation of single-pathway inhibition and supports the need for multi-target or adaptive therapeutic strategies. Current therapies focusing on a single pathway underestimate the high plasticity of septic cells. Targeting intratumoral heterogeneity or stem-like protective cells, such as MSCs acting as biological rheostats, has been proposed as a novel strategy to overcome treatment resistance (135).

The full list of agents targeting apoptotic caspase-mediated pyroptosis is synthesized in Table IV. Table IV summarizes inhibitors of the apoptotic caspase-mediated pathway in S-ALI, detailing targeting nodes (primarily caspase-3, caspase-8 and caspase-9), representative agents (e.g., irisin, resveratrol, ligustrazine, MSCs), molecular mechanisms and key outcomes in murine models, such as reduced caspase-3 activity, reduced lung injury, reduced microvascular permeability and reduced epithelial pyroptosis, along with associated risks and limitations.

Human evidence, ongoing/completed trials, and translational challenges. Although human evidence for the modulation of pyroptosis in S-ALI remains limited, it is increasingly promising. Circulating GSDMD fragments, IL-1β, IL-18 and inflammasome-associated signatures have been reported to be elevated in patients with sepsis in the ICU and in COVID-19-associated ARDS (56,136). Notably, these signals appear to be more prominent in hyperinflammatory bacterial sepsis than in certain viral ARDS cohorts, suggesting

Table IV. Inhibition of the apoptotic caspases-mediated pathway of pyroptosis for the treatment of S-ALI.

Targeting node	Representative agents	Inducer	Molecular mechanism and orchestration	Evidence level and key outcomes	Risks/limitations	(Refs.)
Caspase-3	Irisin	LPS	Activates AMPK/SIRT1 to downregulate p66Shc and caspase-3	Murine: Reduced microvascular permeability	Limited human data	(181)
Caspase-3/9	ERRα	LPS	Ameliorates endothelial hyperpermeability and reduces cleaved caspase-3/9	Murine: Reduced adherens junction degradation	Gene-level modulation	(182)
Caspase-3/8	Dulaglutide	LPS	Reduces caspase-3, cleaved caspase-3, caspase-8 and Bcl-2/Bax ratio	Murine: Reduced lung injury, reduced cytokines, reduced neutrophil infiltration	Metabolic effects	(183)
Caspase-3	miR-128-3p	*In vitro*: LPS; *In vivo*: CLP	Suppresses caspase-3 activation	Murine + cell: Reduced caspase-3 activity and ALI	MicroRNA delivery challenges	(184)
Caspase-3	Resveratrol	CLP	Reduces activated caspase-3 protein	Murine: Reduced caspase-3 levels	Bioavailability issues	(185)
Caspase-8	Breviscapine	CLP	Downregulates caspase-8 expression and activity	Murine: Triggers neutrophil apoptosis	Limited human data	(186)
Multi-caspase	Dexmedetomidine	CLP	Ameliorates activity of caspase-3, -8, -9	Murine: reduced caspase activities	Sedative effects	(187)
Caspase-3/8	Ligustrazine	LPS	Inhibits TLR4/TRAF6/NF-κB/NLRP3/ caspase-1 and TLR4/caspase-8/ caspase-3 pathways	Murine: Reduced pyroptosis and macrophage polarization reversal	Limited clinical experience	(133)
Caspase-3-GSDME	Mesenchymal stem cells	Intranasal MA01	Inhibits caspase-3-GSDME-mediated pyroptosis	Murine: Reduced epithelial pyroptosis	Cell therapy variability	(188)
Caspase-3	Coptisine	LPS	Inhibits Bax and cleaved caspase-3	Murine: Reduced caspase-3 expression	Herbal standardization	(189)
Caspase-3	Artemisinin	LPS	Inhibits caspase-3 pathway	Murine: Reduced caspase-3, TNF-α, and IL-6	Limited sepsis-specific data	(190)
Caspase-3	Ginsenoside Rg1	CLP	Reduces caspase-3 expression	Murine: Reduced caspase-3, reduced cytokines, reduced mortality	Limited human data	(191)
Caspase-3	Protopine	CLP/LPS (BEAS-2B)	Reduces cleaved caspase-3 and Cyto C; increases Bcl-2/Bax	Murine + cell: Reduced pyroptosis-associated proteins	Limited clinical translation	(192)
Caspase-3/9	Lianhua Qingwen	LPS	Decreases Bax, caspase-3 and caspase-9 levels	Murine: Reduced septic ALI	Herbal mixture standardization	(193)

S-ALI, sepsis-induced acute lung injury; caspase-3, cysteine-aspartic protease-3; caspase-8, cysteine-aspartic protease-8; caspase-9, cysteine-aspartic protease-9; GSDME, gasdermin E; AMPK, AMP-activated protein kinase; SIRT1, sirtuin 1; p66Shc, Src homology 2 domain-containing transforming protein C1 isoform p66; ERRα, estrogen-related receptor α; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6; NF-κB, nuclear factor kappa B; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; Cyto C, cytochrome c; TNF-α, tumor necrosis factor alpha; IL, interleukin; LPS, lipopolysaccharide; CLP, cecal ligation and puncture; ALI, acute lung injury; BEAS-2B, human bronchial epithelial cell line; MA01, murine alveolar macrophage cell line; miR-128-3p, microRNA-128-3p; MSCs, mesenchymal stromal cells.

substantial inflammatory heterogeneity across patient populations (137).

Current biomarker-guided studies and key translational and clinical investigations targeting complement-inflammasome-pyroptosis-associated pathways have begun to provide early, yet heterogeneous evidence for clinical efficacy in critically ill patients. In particular, vilobelimab (anti-C5a monoclonal antibody) has been evaluated in randomized clinical trials in severe COVID-19-associated ARDS, where treatment was shown to be associated with a reduction in 28-day mortality and trends toward improved ventilator-free days in selected hyperinflammatory subgroups, although overall effects across unselected populations remained variable (138,139).

In addition to vilobelimab, earlier clinical attempts to broadly suppress inflammatory injury in sepsis and ARDS, without targeting specific pyroptosis-related pathways or applying biomarker-based stratification, have largely failed to demonstrate consistent improvements in mortality or organ failure scores, highlighting the limitations of non-selective anti-inflammatory approaches in critical illness. These findings collectively indicate that the therapeutic modulation of pyroptosis-related signaling requires both pathway specificity and patient stratification to achieve clinical efficacy.

Among candidate therapeutic nodes, upstream NLRP3 inflammasome blockade may provide the broader suppression of caspase-1 activation, IL-1β/IL-18 maturation and downstream pyroptotic amplification during the early hyperinflammatory stage of S-ALI (140). By contrast, direct GSDMD inhibition may more specifically prevent membrane pore formation and terminal cell lysis, while preserving part of the upstream immune sensing cascade (9). The modulation of the IL-1 pathway represents a downstream anti-inflammatory strategy that may attenuate cytokine-driven tissue injury, but does not completely suppress inflammasome activation or pyroptotic execution (141). Compared with conventional broad-spectrum anti-inflammatory therapies, pyroptosis-targeted interventions provide the potential advantage of mechanism-guided precision modulation by directly interrupting regulated inflammatory cell death pathways closely linked to alveolar barrier disruption, endothelial leakage, and maladaptive innate immune amplification in S-ALI (140).

Among the currently available translational strategies, substantial heterogeneity exists regarding both mechanistic specificity and clinical applicability. Upstream inflammasome-directed approaches, such as NLRP3 inhibition, may provide the broader suppression of caspase-1 activation and downstream cytokine maturation during the early hyperinflammatory phase; however, they may also increase the risk of excessive immune suppression when administered during later septic stages (142). By contrast, downstream IL-1 pathway blockade appears to represent a comparatively safer and clinically feasible strategy, particularly in biomarker-enriched hyperinflammatory subgroups, as illustrated by anakinra-related research (129). Complement-targeted interventions, such as vilobelimab may be particularly relevant in endothelial-dominant inflammatory phenotypes characterized by excessive C5a activation and neutrophil-driven tissue injury (138). Notably, several translational studies summarized in Table V have demonstrated that non-stratified anti-inflammatory interventions have frequently failed to achieve consistent survival benefits, highlighting that therapeutic efficacy is highly dependent on appropriate endotype selection, the timing of intervention and the preservation of essential host defense mechanisms. Collectively, current evidence supports a transition from empiric broad immunosuppression toward biomarker-guided precision modulation of pyroptosis-associated inflammatory pathways in S-ALI.

Notably, a substantial proportion of currently available human evidence is derived from COVID-19-associated ARDS cohorts rather than classical bacterial sepsis-induced ALI (137). Although these studies provide valuable proof-of-concept support for inflammasome and pyroptosis modulation, significant differences exist between viral and bacterial inflammatory programs, including pathogen-recognition pathways, neutrophil predominance, complement activation patterns and immune exhaustion trajectories (137). Therefore, caution is required when extrapolating COVID-19-based findings directly to heterogeneous sepsis populations.

Nevertheless, a substantial discordance persists between robust preclinical efficacy and relatively modest clinical outcomes. This discrepancy may partly reflect the dual role of pyroptosis in host defense and tissue injury, the existence of narrow therapeutic timing windows and the marked immunological plasticity observed during different stages of sepsis (143). A number of experimental inhibitors fail to translate clinically as they insufficiently account for patient stratification, inflammatory endotype, and stage-specific immune status. Patients with excessive inflammasome activation or elevated circulating IL-1β/IL-18 signatures may represent the most plausible candidates for pyroptosis-targeted interventions. Based on these signals, a biomarker-guided stratification framework may be used to identify a 'pyroptosis-high' inflammatory subphenotype in patients with S-ALI/ARDS (144), whereas inappropriate late-stage suppression could potentially aggravate sepsis-associated immunosuppression. A biomarker-guided stratification framework for S-ALI is defined as follows: Candidate pyroptosis-related biomarkers include circulating GSDMD cleavage products (GSDMD p30), IL-1β and IL-18, primarily measured in plasma or serum samples obtained within 24-48 h of admission to the ICU (9). Bronchoalveolar lavage fluid may be used in research settings; however, is not routinely feasible in critically ill patients. Real-world application is constrained by delayed laboratory turnaround time, variability in sampling timing, and dynamic changes in inflammatory status over the disease course. Biomarker interpretation should also consider confounding factors, such as acute kidney injury, extracorporeal membrane oxygenation and multi-organ dysfunction, which may significantly alter circulating inflammatory profiles (145).

Based on this framework, patients can be stratified into hyperinflammatory pyroptosis-high and hypo-inflammatory endotypes to support mechanism-guided therapeutic selection (9). In the early hyperinflammatory phase, characterized by elevated levels of GSDMD p30, IL-1β, and IL-18, therapeutic strategies are primarily directed toward inhibition of the canonical inflammasome axis, including NLRP3 and caspase-1 blockade, as well as downstream IL-1 signaling modulation. By contrast, in later stages or in patients progressing toward immunosuppression, excessive inflammasome inhibition should be avoided, and supportive or

Table V. Human evidence and clinical trials for pyroptosis-related interventions for S-ALI.

Intervention/ target	Agent/ approach	Trial phase/ design	Population (etiology)	Mechanistic pathway (pyroptosis axis)	Target engagement/ biomarkers	Patient endotypes/ stratification	Risks/limitations	(Refs.)
Circulating GSDMD (biomarker)	Detection of active GSDMD (p30)	Observational	Sepsis/ICU admission	Gasdermin-mediated pyroptotic execution activation	Plasma GSDMD-NT (p30)	Pyroptosis-high inflammatory signature phenotype (exploratory biomarker-defined endotype)	Confounded by AKI/ECMO	(121)
Inflammasome activation	NLRP3/ caspase-1/ GSDMD	Observational	Severe SARS-CoV-2/ARDS	Canonical inflammasome activation in myeloid cells	NLRP3 expression, cleaved caspase-1 (p20), GSDMD-NT, IL-1β, IL-18	Virus-associated inflammatory ARDS endotype with inflammasome activation	Observational; etiology-specific (COVID-19)	(122)
NLRP3 inhibitor (translational)	GDC-2394 (oral)	First-in-human PK/PD and safety	Healthy volunteers	NLRP3 inflammasome blockade (upstream inhibition)	Suppression of plasma IL-1β and IL-18	No patient stratification (non-endotype specific early phase study)	Development halted due to safety signals	(127)
IL-1 receptor antagonism	Anakinra (IL-1RA)	Biomarker-guided RCT/ post-hoc	Hyperinflammatory sepsis/ suPAR-guided COVID-19	IL-1-mediated downstream pyroptosis amplification blockade	Reduction in IL-1β, IL-18, suPAR, IL-6	Hyperinflammatory endotype (suPAR-high/ cytokine-high subgroup)	Immunosuppression risk	(3)
NLRP3 inhibition	DFV890 (oral)	Phase 2	COVID-19 pneumonia/ respiratory dysfunction	Selective inflammasome inhibition at NLRP3 level	Decreased NLRP3 activity, reduced IL-1β and IL-18	Inflammasome-activated respiratory failure endotype	Early-stage; mainly COVID-19	(125)
Mesenchymal stromal cells	MSCs	Multiple RCTs	ARDS/COVID-19 ARDS/severe respiratory failure	Broad immunomodulation of inflammasome and cytokine networks	Reduction in plasma IL-1β, IL-18 and GSDMD-NT	Heterogeneous ARDS inflammatory endotype (non-stratified in most trials)	Inconsistent hard endpoints	(194,195)
Alpha-1 antitrypsin	AAT (IV)	Multicenter early/exploratory RCT	Moderate to severe COVID-19 ARDS	Anti-inflammatory modulation of innate immune activation	Decreased IL-1β, IL-6, and neutrophil activation markers	Systemic inflammatory ARDS phenotype (broad endotype)	Indirect effect on pyroptosis	(196)
VIP analogue	Aviptadil (IV or inhaled)	Small-scale RCT/open-label	COVID-19 ARDS/respiratory failure	Cytoprotective modulation of inflammatory cell death pathways	Reduced IL-1β, IL-18, and LDH	Severe respiratory failure inflammatory endotype	Small sample size; preliminary	(197)

S-ALI, sepsis-induced acute lung injury; GSDMD, gasdermin D; GSDMD-NT, N-terminal fragment of gasdermin D; p30, cleaved active fragment of GSDMD; NLRP3, NOD-like receptor family pyrin domain containing 3; IL, interleukin; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; IL-1RA, interleukin-1 receptor antagonist; suPAR, soluble urokinase plasminogen activator receptor; caspase-1, cysteine-aspartic protease-1; DFV890, selective NLRP3 inhibitor; GDC-2394, NLRP3 inflammasome inhibitor; MSCs, mesenchymal stromal cells; ARDS, acute respiratory distress syndrome; COVID-19 ARDS, coronavirus disease 2019-associated acute respiratory distress syndrome; AAT, alpha-1 antitrypsin; VIP, vasoactive intestinal peptide; PK/PD, pharmacokinetics/pharmacodynamics; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; LDH, lactate dehydrogenase.

immune-restorative approaches may be more appropriate (9). In endothelial-predominant injury phenotypes, targeting the C5a-complement axis may provide additional benefit, whereas in mixed or highly plastic PANoptotic states, combination or multi-target strategies are likely required to achieve effective disease control (134).

To provide a coherent overview of translational readiness, representative human studies and ongoing or terminated clinical trials relevant to pyroptosis-modulating strategies in sepsis, ARDS and S-ALI are summarized in Table V.

Table V summarizes human evidence and clinical trials for pyroptosis-related interventions in S-ALI. It details various interventions/targets (e.g., circulating GSDMD as biomarker, NLRP3 inhibitors, anakinra, MSCs and vilobelimab), trial phases, target populations, mechanistic pathways, specific biomarkers for target engagement (such as plasma GSDMD-NT, IL-1β and IL-18), patient endotype stratification frameworks, as well as risks and limitations of each approach.

Of note, these studies collectively demonstrate that successful clinical translation depends not only on pathway inhibition itself, but also on appropriate patient stratification, inflammatory endotype characterization, therapeutic timing and the preservation of antimicrobial host defense.

5. Challenges and future perspectives

Targeting pyroptosis in S-ALI presents intrinsic challenges that arise from the dual role of inflammatory cell death in host defense and tissue injury. Controlled activation contributes to pathogen clearance and immune surveillance, whereas dysregulated or sustained activation amplifies inflammatory cascades, disrupts alveolar-capillary barrier integrity and accelerates organ dysfunction. This dual nature makes indiscriminate or prolonged suppression of pyroptotic signaling potentially detrimental to immune competence and infection control (146). The molecular heterogeneity of pyroptosis further complicates therapeutic translation, as distinct inflammasome sensors, upstream caspases and gasdermin family members are differentially engaged across disease stages, cell populations and inflammatory microenvironments, leading to context-dependent outcomes that are not adequately captured by single-pathway inhibition strategies (147). In the setting of sepsis, dynamic shifts in immune status occur over time, with early hyperinflammation frequently transitioning toward immunosuppression, indicating that the timing and intensity of pyroptosis modulation are likely to determine therapeutic efficacy and safety rather than simple pathway blockade (148). Notably, a number of candidate inhibitors targeting the NLRP3-caspase-1-GSDMD axis, including MCC950 and VX-765, have demonstrated substantial efficacy in murine LPS or CLP models, but remain limited in clinical translation due to insufficient pharmacokinetic validation, heterogeneous patient responses and concerns regarding excessive suppression of antimicrobial immunity (149,150). For example, it was previously demonstrated that MCC950 (50 mg/kg) significantly reduced neutrophil infiltration, IL-1β/IL-18 levels and lung injury, scores and improved the survival of mice with LPS-induced ALI and CLP-induced sepsis (151). Similarly, VX-765 attenuated caspase-1-mediated pyroptosis and lung injury in murine models of LPS-induced ALI, although its protective effects were incomplete due to pathway compensation (5). This heterogeneity is largely driven by differences in underlying inflammatory endotypes (e.g., hyperinflammatory endotype with high IL-6/IL-8 showing better response to NLRP3 inhibition vs. hypoinflammatory endotype), the timing of intervention relative to disease stage (early administration protective in LPS models, but detrimental in late immunosuppressive phase of CLP sepsis), variability in baseline comorbidities (e.g., obesity and diabetes causing exaggerated NLRP3 priming and worse outcomes), genetic polymorphisms in inflammasome-related genes (e.g., NLRP3 gain-of-function variants rs35829419 associated with higher IL-1β production and severe ARDS), and pathogen-specific factors (stronger NLRP3 activation in Gram-negative vs. Gram-positive infections), resulting in highly variable target engagement and therapeutic responses across patients in the ICU (152).

Since basal pyroptotic signaling contributes to intracellular pathogen clearance and innate immune surveillance, indiscriminate or prolonged inhibition may inadvertently increase susceptibility to secondary infection and late-stage immune paralysis in critically ill patients (144). These findings collectively suggest that the successful clinical application of pyroptosis-targeted therapies will likely require biomarker-guided patient stratification and stage-specific intervention rather than uniform pathway inhibition across all phases of sepsis-associated acute lung injury (144).

From a translational perspective, the majority of currently available evidence supporting pyroptosis inhibition in S-ALI is derived from experimental models that only partially reproduce the clinical complexity of sepsis, including inter-individual variability, comorbid conditions and heterogeneous infectious sources, which collectively influence inflammatory trajectories and treatment responsiveness (153). Differences in species-specific inflammasome regulation, gasdermin expression patterns and immune cell composition further limit the direct extrapolation of preclinical findings to critically ill patients (146). Clinical observations have shown that patients with sepsis-associated ARDS exhibit elevated levels of inflammasome-associated biomarkers, such as IL-1β and IL-18, and preliminary interventional studies using inflammasome-targeted agents are being explored in ARDS cohorts with elevated caspase-1 activity, providing early human evidence linking inflammasome modulation to lung inflammation in acute respiratory failure (154). Furthermore, serum concentrations of NLRP3 are significantly higher in patients with sepsis who develop ARDS, and are associated with disease severity and 28-day mortality, suggesting that inflammasome activation markers have clinical diagnostic and prognostic value in human S-ALI (21). Emerging clinical data also indicate that an elevated expression of NLRP3 in patients with ARDS is associated with worse oxygenation and organ dysfunction scores, highlighting the translational relevance of inflammasome-related cell death pathways in human lung injury (155).

In addition, pyroptosis does not occur in isolation but intersects with apoptosis, necroptosis, autophagy and metabolic reprogramming, forming an integrated cell death network in which the selective modulation of a single node may trigger compensatory mechanisms that sustain inflammation or tissue

damage, underscoring the need for a systems-level understanding of regulated cell death in septic lung injury (156). Observational clinical analyses using single-cell transcriptomics and pyroptosis-related gene signatures have stratified patients with sepsis-induced ARDS into prognostic groups based on immune cell composition and pyroptosis signaling profiles, supporting the potential for personalized approaches to targeting regulated cell death in human disease (157).

Future research is thus warranted to focus on refining the precision of pyroptosis-targeted interventions by integrating disease stage, cellular specificity and host immune status into therapeutic design. The identification of reliable biomarkers reflecting pyroptotic activity in lung tissue and circulation may enable the stratification of patients who are most likely to benefit from targeted modulation, while avoiding unnecessary immune suppression in others (158). Advances in multi-omics profiling, spatial transcriptomics and single-cell analyses are expected to provide deeper insight into cell type-specific pyroptotic responses and their temporal evolution during sepsis (158). Therapeutic strategies that achieve the balanced regulation rather than the complete inhibition of pyroptosis, particularly approaches that preserve antimicrobial defense, while limiting inflammatory amplification and barrier disruption, may provide a more viable path toward clinical application (75). Through the continued integration of mechanistic research with translational and clinical investigation, targeting pyroptosis holds promise for improving outcomes in S-ALI, while aligning with the broader goal of individualized management in critical care medicine (75).

6. Conclusion

In summary, pyroptosis represents a pivotal and actionable programmed cell death mode that drives the biological and clinical heterogeneity of S-ALI. The transition from a single-pathway model to an integrated landscape involving canonical, non-canonical and PANoptosome-mediated signaling has redefined the understanding of pulmonary inflammatory amplification. While preclinical studies have identified a vast repertoire of pharmacological agents, the path to clinical translation hinges on the shift from 'one-size-fits-all' strategies to biomarker-guided, stage-specific interventions. By integrating high-resolution molecular signatures with individual patient endotypes, targeting the pyroptotic cascade provides a promising frontier for achieving precision-guided management and improving the survival of critically ill patients with sepsis-induced respiratory failure.

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Availability of data and materials

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Authors' contributions

WW was involved in the conceptualization of the study, analysis and tge interpretation of published literature, visualization and validation, and the drafting of the manuscript. NL and GD were involved in the literature search, screening, extraction, the synthesis of published evidence, validation and visualization. SY, RC and RZ contributed to the preparation of the manuscript, reference checking and content organization, and provided administrative support. JL was responsible for the study design, project administration, supervision, funding acquisition, quality control of the manuscript, critical revision of the intellectual content, and manuscript review and editing. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cajander S, Kox M, Scicluna BP, Weigand MA, Mora RA, Flohe SB, Martin-Loeches I, Lachmann G, Girardis M, Garcia-Salido A, *et al*: Profiling the dysregulated immune response in sepsis: Overcoming challenges to achieve the goal of precision medicine. Lancet Respir Med 12: 305-322, 2024.
2. Moore AR, Pienkos SM, Sinha P, Guan J, O'Kane CM, Levitt JE, Wilson JG, Shankar-Hari M, Matthay MA, Calfee CS, *et al*: Elevated plasma interleukin-18 identifies high-risk acute respiratory distress syndrome patients not distinguished by prior latent class analyses using traditional inflammatory cytokines: A retrospective analysis of two randomized clinical trials. Crit Care Med 51: e269-e274, 2023.
3. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ and Opal SM: Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: Reanalysis of a prior phase iii trial. Crit Care Med 44: 275-281, 2016.
4. Li Z, Wang Y, Feng Q, Zhang Y, Zhuang Y, Xie Z and Bai X: Inhibition of the c3a receptor attenuates sepsis-induced acute lung injury by suppressing pyroptosis of the pulmonary vascular endothelial cells. Free Radic Biol Med 184: 208-217, 2022.
5. Li H, Guan Y, Liang B, Ding P, Hou X, Wei W and Ma Y: Therapeutic potential of MCC950, a specific inhibitor of NLRP3 inflammasome. Eur J Pharmacol 928: 175091, 2022.

6. Darkwah S, Kotey F, Ahenkorah J, Adutwum-Ofosu KK and Donkor ES: Sepsis-related lung injury and the complication of extrapulmonary pneumococcal pneumonia. Diseases 12: 72, 2024.
7. GBD 2021 Global Sepsis Collaborators: Global, regional, and national sepsis incidence and mortality, 1990-2021: A systematic analysis. Lancet Globa Health 13: e2013-e2026, 2025.
8. Wang D, Jia H, Zheng X, Xi X, Zheng Y and Li W: Attributable mortality of ARDS among critically ill patients with sepsis: A multicenter, retrospective cohort study. BMC Pulm Med 24: 110, 2024.
9. Wang Z, Li X, Yuan B and Zhang J: Gasdermin D-driven pyroptosis in sepsis: Mechanisms, therapeutic strategies, and clinical translation. Front Immunol 17: 1801896, 2026.
10. Ding Z, Zhong R, Yang Y, Xia T, Wang W, Wang Y, Xing N, Luo Y, Li S, Shang L and Shu Z: Systems pharmacology reveals the mechanism of activity of Ge-Gen-Qin-Lian decoction against LPS-induced acute lung injury: A novel strategy for exploring active components and effective mechanism of TCM formulae. Pharmacol Res 156: 104759, 2020.
11. Zheng Y, Wang J, Ling Z, Zhang J, Zeng Y, Wang K, Zhang Y, Nong L, Sang L, Xu Y, *et al*: A diagnostic model for sepsis-induced acute lung injury using a consensus machine learning approach and its therapeutic implications. J Transl Med 21: 620, 2023.
12. Kumar V: Pulmonary innate immune response determines the outcome of inflammation during pneumonia and sepsis-associated acute lung injury. Front Immunol 11: 1722, 2020.
13. Dolmatova EV, Forrester SJ, Wang K, Ou Z, Williams HC, Joseph G, Kumar S, Valdivia A, Kowalczyk AP, Qu H, *et al*: Endothelial poldip2 regulates sepsis-induced lung injury via rho pathway activation. Cardiovasc Res 118: 2506-2518, 2022.
14. Parker JC: Acute lung injury and pulmonary vascular permeability: Use of transgenic models. Compr Physiol 1: 835-882, 2011.
15. Long ME, Mallampalli RK and Horowitz JC: Pathogenesis of pneumonia and acute lung injury. Clin Sci (Lond) 136: 747-769, 2022.
16. Li W, Li D, Chen Y, Abudou H, Wang H, Cai J, Wang Y, Liu Z, Liu Y and Fan H: Classic signaling pathways in alveolar injury and repair involved in sepsis-induced ALI/ARDS: New research progress and prospect. Dis Markers 2022: 6362344, 2022.
17. Zhang F, Guo F, Zhang Y, Xu H, Liu Y, Lin L, Li H, Yang H and Huang L: Huashibaidu formula attenuates sepsis-induced acute lung injury via suppressing cytokine storm: Implications for treatment of COVID-19. Phytomedicine 109: 154549, 2023.
18. von During S, Liu K, Munshi L, Kim SJ, Urner M, Adhikari NK, Parhar K and Fan E: The association between mechanical power within the first 24 hours and ICU mortality in mechanically ventilated adult patients with acute hypoxemic respiratory failure: A registry-based cohort study. Chest 168: 901-911, 2025.
19. Antimicrobial Resistance Collaborators: Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet 399: 629-655, 2022.
20. Coll RC, Schroder K and Pelegrin P: NLRP3 and pyroptosis blockers for treating inflammatory diseases. Trends Pharmacol Sci 43: 653-668, 2022.
21. Yang Q, Zhang X, Luo L and Shen J: Clinical application of serum NLRP3 on the diagnosis and prognosis of sepsis patients complicated with acute respiratory distress syndrome. Front Immunol 14: 1205132, 2023.
22. Fink SL and Cookson BT: Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages. Cell Microbiol 8: 1812-1825, 2006.
23. Fink SL and Cookson BT: Pyroptosis and host cell death responses during salmonella infection. Cell Microbiol 9: 2562-2570, 2007.
24. Zhang YY and Ning BT: Signaling pathways and intervention therapies in sepsis. Signal Transduct Target Ther 6: 407, 2021.
25. Dolmatova EV, Wang K, Mandavilli R and Griendling KK: The effects of sepsis on endothelium and clinical implications. Cardiovasc Res 117: 60-73, 2021.
26. Joffre J, Hellman J, Ince C and Ait-Oufella H: Endothelial responses in sepsis. Am J Respir Crit Care Med 202: 361-370, 2020.
27. Zhang H, Wang Y, Qu M, Li W, Wu D, Cata JP and Miao C: Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. Clin Transl Med 13: e1170, 2023.
28. Zheng X, Chen W, Gong F, Chen Y and Chen E: The role and mechanism of pyroptosis and potential therapeutic targets in sepsis: A review. Front Immunol 12: 711939, 2021.
29. Mei Y, Chen X, Shi S, Lin W, Cheng Z, Fan X, Wu W, Han J, Huang W, Ye B and Dai S: GI-Y2, a novel gasdermin D inhibitor, attenuates sepsis-induced myocardial dysfunction by inhibiting gasdermin D-mediated pyroptosis in macrophages. Br J Pharmacol 182: 3503-3521, 2025.
30. Kasana S, Kumar S, Patel P, Kurmi BD, Jain S, Sahu S and Vaidya A: Caspase inhibitors: A review on recently patented compounds (2016-2023). Expert Opin Ther Pat 34: 1047-1072, 2024.
31. Joshi GP, Kehlet H and Lobo DN: Nonsteroidal anti-inflammatory drugs in the perioperative period: Current controversies and concerns. Br J Anaesth 134: 294-296, 2025.
32. Li Y, Hu C, Zhai P, Zhang J, Jiang J, Suo J, Hu B, Wang J, Weng X, Zhou X, *et al*: Fibroblastic reticular cell-derived exosomes are a promising therapeutic approach for septic acute kidney injury. Kidney Int 105: 508-523, 2024.
33. Tao H, Zhao H, Mo A, Shao L, Ge D, Liu J, Hu W, Xu K, Ma Q, Wang W, *et al*: VX-765 attenuates silica-induced lung inflammatory injury and fibrosis by modulating alveolar macrophages pyroptosis in mice. Ecotoxicol Environ Saf 249: 114359, 2023.
34. Fontana P, Du G, Zhang Y, Zhang H, Vora SM, Hu JJ, Shi M, Tufan AB, Healy LB, Xia S, *et al*: Small-molecule GSDMD agonism in tumors stimulates antitumor immunity without toxicity. Cell 187: 6165-6181, 2024.
35. Vasudevan SO, Behl B and Rathinam VA: Pyroptosis-induced inflammation and tissue damage. Semin Immunol 69: 101781, 2023.
36. Cao Z, Li W, Shao Z, Liu X, Zeng Y, Lin P, Lin C, Zhao Y, Li T, Zhao Z, *et al*: Apelin ameliorates sepsis-induced myocardial dysfunction via inhibition of NLRP3-mediated pyroptosis of cardiomyocytes. Heliyon 10: e24568, 2024.
37. Gu L, Sun M, Li R, Zhang X, Tao Y, Yuan Y, Luo X and Xie Z: Didymin suppresses microglia pyroptosis and neuroinflammation through the Asc/caspase-1/GSDMD pathway following experimental intracerebral hemorrhage. Front Immunol 13: 810582, 2022.
38. Feng Y, Li M, Yangzhong X, Zhang X, Zu A, Hou Y, Li L and Sun S: Pyroptosis in inflammation-related respiratory disease. J Physiol Biochem 78: 721-737, 2022.
39. Ma X, Hao J, Wu J, Li Y, Cai X and Zheng Y: Prussian blue nanozyme as a pyroptosis inhibitor alleviates neurodegeneration. Adv Mater 34: e2106723, 2022.
40. Zhao P, Yin S, Qiu Y, Sun C and Yu H: Ferroptosis and pyroptosis are connected through autophagy: A new perspective of overcoming drug resistance. Mol Cancer 24: 23, 2025.
41. Loveless R, Bloomquist R and Teng Y: Pyroptosis at the forefront of anticancer immunity. J Exp Clin Cancer Res 40: 264, 2021.
42. Kesavardhana S, Malireddi R and Kanneganti TD: Caspases in cell death, inflammation, and pyroptosis. Annu Rev Immunol 38: 567-595, 2020.
43. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G and Alnemri ES: Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. Nat Commun 8: 14128, 2017.
44. Zheng D, Liwinski T and Elinav E: Inflammasome activation and regulation: Toward a better understanding of complex mechanisms. Cell Discov 6: 36, 2020.
45. Xu H, Yang J, Gao W, Li L, Li P, Zhang L, Gong YN, Peng X, Xi JJ, Chen S, *et al*: Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. Nature 513: 237-241, 2014.
46. Wu J, Fernandes-Alnemri T and Alnemri ES: Involvement of the AIM2, NLRC4, and NLRP3 inflammasomes in caspase-1 activation by Listeria monocytogenes. J Clin Immunol 30: 693-702, 2010.
47. Ting JP, Lovering RC, Alnemri ES, Bertin J, Boss JM, Davis BK, Flavell RA, Girardin SE, Godzik A, Harton JA, *et al*: The NLR gene family: A standard nomenclature. Immunity 28: 285-287, 2008.
48. Mitchell PS, Sandstrom A and Vance RE: The NLRP1 inflammasome: New mechanistic insights and unresolved mysteries. Curr Opin Immunol 60: 37-45, 2019.
49. Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E and Fitzgerald KA: AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature 458: 514-518, 2009.
50. Elliott EI and Sutterwala FS: Initiation and perpetuation of NLRP3 inflammasome activation and assembly. Immunol Rev 265: 35-52, 2015.
51. Kahlenberg JM and Dubyak GR: Mechanisms of caspase-1 activation by P2X7 receptor-mediated K+ release. Am J Physiol Cell Physiol 286: C1100-C1108, 2004.

52. Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A, Warren SE, Wewers MD and Aderem A: Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol 11: 1136-1142, 2010.
53. Kayagaki N, Warming S, Lamkanfi M, Vande WL, Louie S, Dong J, Newton K, Qu Y, Liu J, Heldens S, *et al*: Non-canonical inflammasome activation targets caspase-11. Nature 479: 117-121, 2011.
54. Man SM and Kanneganti TD: Regulation of inflammasome activation. Immunol Rev 265: 6-21, 2015.
55. Shi J, Zhao Y, Wang Y, Gao W, Ding J, Li P, Hu L and Shao F: Inflammatory caspases are innate immune receptors for intracellular LPS. Nature 514: 187-192, 2014.
56. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, Cuellar T, Haley B, Roose-Girma M, Phung QT, *et al*: Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature 526: 666-671, 2015.
57. Ruhl S and Broz P: Caspase-11 activates a canonical NLRP3 inflammasome by promoting k(+) efflux. Eur J Immunol 45: 2927-2936, 2015.
58. Yang D, He Y, Munoz-Planillo R, Liu Q and Nunez G: Caspase-11 requires the Pannexin-1 channel and the Purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. Immunity 43: 923-932, 2015.
59. Eskandari E and Eaves CJ: Paradoxical roles of caspase-3 in regulating cell survival, proliferation, and tumorigenesis. J Cell Biol 221: e202201159, 2022.
60. Jiang M, Qi L, Li L and Li Y: The caspase-3/GSDME signal pathway as a switch between apoptosis and pyroptosis in cancer. Cell Death Discov 6: 112, 2020.
61. Zhang Z, Zhang Y, Xia S, Kong Q, Li S, Liu X, Junqueira C, Meza-Sosa KF, Mok T, Ansara J, *et al*: Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature 579: 415-420, 2020.
62. Rogers C, Erkes DA, Nardone A, Aplin AE, Fernandes-Alnemri T and Alnemri ES: Gasdermin pores permeabilize mitochondria to augment caspase-3 activation during apoptosis and inflammasome activation. Nat Commun 10: 1689, 2019.
63. Sarhan J, Liu BC, Muendlein HI, Li P, Nilson R, Tang AY, Rongvaux A, Bunnell SC, Shao F, Green DR and Poltorak A: Caspase-8 induces cleavage of gasdermin D to elicit Pyroptosis during Yersinia infection. Proc Natl Acad Sci USA 115: E10888-E10897, 2018.
64. Keller N, Mares J, Zerbe O and Grutter MG: Structural and biochemical studies on procaspase-8: New insights on initiator caspase activation. Structure 17: 438-448, 2009.
65. Fritsch M, Gunther SD, Schwarzer R, Albert MC, Schorn F, Werthenbach JP, Schiffmann LM, Stair N, Stocks H, Seeger JM, *et al*: Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. Nature 575: 683-687, 2019.
66. Lu X, Guo T and Zhang X: Pyroptosis in cancer: Friend or foe? Cancers (Basel) 13: 3620, 2021.
67. Chowdhury D and Lieberman J: Death by a thousand cuts: Granzyme pathways of programmed cell death. Annu Rev Immunol 26: 389-420, 2008.
68. Metkar SS, Menaa C, Pardo J, Wang B, Wallich R, Freudenberg M, Kim S, Raja SM, Shi L, Simon MM, *et al*: Human and mouse granzyme A induce a proinflammatory cytokine response. Immunity 29: 720-733, 2008.
69. Joeckel LT and Bird PI: Are all granzymes cytotoxic in vivo? Biol Chem 395: 181-202, 2014.
70. Wensink AC, Hack CE and Bovenschen N: Granzymes regulate proinflammatory cytokine responses. J Immunol 194: 491-497, 2015.
71. Campbell RA, Franks Z, Bhatnagar A, Rowley JW, Manne BK, Supiano MA, Schwertz H, Weyrich AS and Rondina MT: Granzyme A in human platelets regulates the synthesis of proinflammatory cytokines by monocytes in aging. J Immunol 200: 295-304, 2018.
72. van Daalen KR, Reijneveld JF and Bovenschen N: Modulation of inflammation by extracellular Granzyme A. Front Immunol 11: 931, 2020.
73. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, Wang Y, Li D, Liu W, Zhang Y, *et al*: Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. Science 368: eaaz7548, 2020.
74. Wei T, Zhang C and Song Y: Molecular mechanisms and roles of pyroptosis in acute lung injury. Chin Med J (Engl) 135: 2417-2426, 2022.
75. Zhou S, Yang X, Mo K and Ning Z: Pyroptosis and polarization of macrophages in septic acute lung injury induced by lipopolysaccharide in mice. Immun Inflamm Dis 12: e1197, 2024.
76. Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z and Shi X: Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. Criti Care 25: 356, 2021.
77. Chen R, Kang R and Tang D: The mechanism of HMGB1 secretion and release. Exp Mol Med 54: 91-102, 2022.
78. Liu J, Song K, Lin B, Chen Z, Zuo Z, Fang Y, He Q, Yao X, Liu Z, Huang Q and Guo X: HMGB1 promotes neutrophil PD-L1 expression through TLR2 and mediates T cell apoptosis leading to immunosuppression in sepsis. Int Immunopharmacol 133: 112130, 2024.
79. Aglietti RA, Estevez A, Gupta A, Ramirez MG, Liu PS, Kayagaki N, Ciferri C, Dixit VM and Dueber EC: GsdmD p30 elicited by caspase-11 during pyroptosis forms pores in membranes. Proc Natl Acad Sci USA 113: 7858-7863, 2016.
80. Zhou Y, Li P, Goodwin AJ, Cook JA, Halushka PV, Chang E, Zingarelli B and Fan H: Exosomes from endothelial progenitor cells improve outcomes of the lipopolysaccharide-induced acute lung injury. Crit Care 23: 44, 2019.
81. Liu W, Shao R, Zhang S, Jin L, Liu R, Chen P, Hu J, Ma H, Wu B, Liang W, *et al*: Characteristics, predictors and outcomes of new-onset QT prolongation in sepsis: A multicenter retrospective study. Critical Care 28: 115, 2024.
82. Wang Q, Wen W, Zhou L, Liu F, Ren X, Yu L, Chen H and Jiang Z: Ll-37 improves sepsis-induced acute lung injury by suppressing pyroptosis in alveolar epithelial cells. Int Immunopharmacol 129: 111580, 2024.
83. Jiang Y, Gao S, Chen Z, Zhao X, Gu J, Wu H, Liao Y, Wang J and Chen W: Pyroptosis in septic lung injury: Interactions with other types of cell death. Biomed Pharmacother 169: 115914, 2023.
84. Wang J, Xue X, Zhao X, Luo L, Liu J, Dai S, Zhang F, Wu R, Liu Y, Peng C, *et al*: Forsythiaside A alleviates acute lung injury by inhibiting inflammation and epithelial barrier damages in lung and colon through PPAR-γ/RXR-α complex. J Adv Res 60: 183-200, 2024.
85. Pandey A, Li Z, Gautam M, Ghosh A and Man SM: Molecular mechanisms of emerging inflammasome complexes and their activation and signaling in inflammation and pyroptosis. Immunol Rev 329: e13406, 2025.
86. Liu Y, Pan R, Ouyang Y, Gu W, Xiao T, Yang H, Tang L, Wang H, Xiang B and Chen P: Pyroptosis in health and disease: Mechanisms, regulation and clinical perspective. Signal Transduct Target Ther 9: 245, 2024.
87. Chen S, Jiang J, Li T and Huang L: PANoptosis: Mechanism and role in pulmonary diseases. Int J Mol Sci 24: 15343, 2023.
88. Wu S, Li Z, Ye M, Liu C, Liu H, He X, Qin Y, Liang F, Pan L and Lin F: VX765, a Specific Caspase-1 inhibitor, alleviates lung ischemia reperfusion injury by suppressing endothelial pyroptosis and barrier dysfunction. Biomed Res Int 2021: 4525988, 2021.
89. Pandeya A and Kanneganti T: Therapeutic potential of PANoptosis: Innate sensors, inflammasomes, and RIPKs in PANoptosomes. Trends Mol Med 30: 74-88, 2024.
90. Yang Z, Kao X, Huang N, Yuan K, Chen J and He M: Identification and analysis of PANoptosis-related genes in Sepsis-induced lung injury by bioinformatics and experimental verification. J Inflamm Res 17: 1941-1956, 2024.
91. Chen X, He W, Hu L, Li J, Fang Y, Wang X, Xu X, Wang Z, Huang K and Han J: Pyroptosis is driven by non-selective gasdermin-D pore and its morphology is different from MLKL Channel-mediated necroptosis. Cell Res 26: 1007-1020, 2016.
92. Herrmann JB, Muenstermann M, Strobel L, Schubert-Unkmeir A, Woodruff TM, Gray-Owen SD, Klos A and Johswich KO: Complement C5a receptor 1 exacerbates the pathophysiology of *N. meningitidis* sepsis and is a potential target for disease treatment. mBio 9: e01755-e017, 2018.
93. Wang Y, Wang L, Ma S, Cheng L and Yu G: Repair and regeneration of the alveolar epithelium in lung injury. FASEB J 38: e23612, 2024.
94. Shi X, Li T, Liu Y, Yin L, Xiao L, Fu L, Zhu Y, Chen H, Wang K, Xiao X, *et al*: HSF1 protects sepsis-induced acute lung injury by inhibiting NLRP3 inflammasome activation. Front Immunol 13: 781003, 2022.
95. Liu J, Song K, Lin B, Chen Z, Liu Y, Qiu X, He Q, Zuo Z, Yao X, Huang X, *et al*: The suppression of HSPA8 attenuates NLRP3 ubiquitination through SKP2 to promote pyroptosis in sepsis-induced lung injury. Cell Biosci 14: 56, 2024.
96. Fan SY, Zhao ZC, Liu XL, Peng YG, Zhu HM, Yan SF, Liu YJ, Xie Q, Jiang Y and Zeng SZ: Metformin mitigates Sepsis-induced acute lung injury and inflammation in young mice by suppressing the S100A8/A9-NLRP3-IL-1β signaling pathway. J Inflamm Res 17: 3785-3799, 2024.

97. Cao X, Zhao M, Wang X, Lin J, Yang M, Zhong L, Liang L, Yue Y, Du J, Li J, *et al*: Multi-metabolomics and intestine microbiome analysis: YZC extract ameliorates septic-ALI by modulating intestine microbiota to reduce TMAO/NLRP3 signaling. Phytomedicine 130: 155345, 2024.
98. Li J, Bai Y, Tang Y, Wang X, Cavagnaro MJ, Li L, Li Z, Zhang Y and Shi J: A 4-benzene-indol derivative alleviates LPS-induced acute lung injury through inhibiting the NLRP3 inflammasome. Front Immunol 13: 812164, 2022.
99. Yan-Fang Y, Na S, Jing-Lan H, Zhi-Hai Z and Jun-Chao Y: The improvement effect and mechanism of xuebijing injection on acute lung injury induced by sepsis in mice. Progress of Anatomical Sciences, pp1-6, 2024.
100. Ji C, Hao X, Li Z, Liu J, Yan H, Ma K, Li L and Zhang L: Phillyrin prevents sepsis-induced acute lung injury through inhibiting the NLRP3/caspase-1/GSDMD-dependent pyroptosis signaling pathway. Acta Biochim Biophys Sin (Shanghai) 57: 447-462, 2024.
101. Li N, Xiong R, He R, Liu B, Wang B and Geng Q: Mangiferin mitigates Lipopolysaccharide-induced lung injury by inhibiting NLRP3 inflammasome activation. J Inflamm Res 14: 2289-2300, 2021.
102. Ye L, Wang H, Duncan SE, Eigel WN and O'Keefe SF: Antioxidant activities of vine tea (Ampelopsis grossedentata) extract and its Major component dihydromyricetin in soybean oil and cooked ground beef. Food Chem 172: 416-422, 2015.
103. Zhu H, Luo P, Fu Y, Wang J, Dai J, Shao J, Yang X, Chang L, Weng Q, Yang B and He Q: Dihydromyricetin prevents cardiotoxicity and enhances anticancer activity induced by Adriamycin. Oncotarget 6: 3254-3267, 2015.
104. Wang YC, Liu QX, Zheng Q, Liu T, Xu XE, Liu XH, Gao W, Bai XJ and Li ZF: Dihydromyricetin alleviates Sepsis-induced acute lung injury through inhibiting NLRP3 Inflammasome-dependent Pyroptosis in mice model. Inflammation 42: 1301-1310, 2019.
105. Zhang B, Luo L, Xiong S, Xiao Y, Zhang T and Xiang T: Anisodamine hydrobromide ameliorates acute lung injury via inhibiting pyroptosis in murine sepsis model. Immunopharmacol Immunotoxicol 46: 662-671, 2024.
106. He H, Long-Bin L, Yang L, Bin L and Yu Z: Chlorogenic acid attenuates acute lung injury in septic mice via ROS/TXNIP/NLRP3 signaling pathway mediated pyrocytosis pathway. Chin J Pathophysiol 37: 1455-1461, 2021.
107. Zhang J, Wang C, Wang H, Li X, Xu J and Yu K: Loganin alleviates Sepsis-induced acute lung injury by regulating macrophage polarization and inhibiting NLRP3 inflammasome activation. Int Immunopharmacol 95: 107529, 2021.
108. Qin Y, Li W, Liu J, Wang F, Zhou W, Xiao L, Zhou P, Wu F, Chen X, Xu S, *et al*: Andrographolide ameliorates sepsis-induced acute lung injury by promoting autophagy in alveolar macrophages via the RAGE/PI3K/AKT/mTOR pathway. Int Immunopharmacol 139: 112719, 2024.
109. Niu X, He Z, Li W, Wang X, Zhi W, Liu F and Qi L: Immunomodulatory activity of the glycoprotein isolated from the Chinese yam (*Dioscorea opposite* thunb). Phytother Res 31: 1557-1563, 2017.
110. Niu X, Zang L, Li W, Xiao X, Yu J, Yao Q, Zhao J, Ye Z, Hu Z and Li W: Anti-inflammatory effect of Yam Glycoprotein on lipopolysaccharide-induced acute lung injury via the NLRP3 and NF-κB/TLR4 signaling pathway. Int Immunopharmacol 81: 106024, 2020.
111. Yang H, Lv H, Li H, Ci X and Peng L: Oridonin protects LPS-induced acute lung injury by modulating Nrf2-mediated oxidative stress and Nrf2-independent NLRP3 and NF-κB pathways. Cell Commun Signal 17: 62, 2019.
112. Xiong S, Hong Z, Huang LS, Tsukasaki Y, Nepal S, Di A, Zhong M, Wu W, Ye Z, Gao X, *et al*: IL-1β suppression of VE-cadherin transcription underlies sepsis-induced inflammatory lung injury. J Clin Invest 133: e169500, 2023.
113. Liu C, Zhou Y, Tu Q, Yao L, Li J and Yang Z: Alpha-linolenic acid pretreatment alleviates NETs-induced alveolar macrophage pyroptosis by inhibiting Pyrin inflammasome activation in a mouse model of sepsis-induced ALI/ARDS. Front Immunol 14: 1146612, 2023.
114. Dong Y, Zhang L, Jiang Y, Dai J, Tang L and Liu G: Emodin reactivated autophagy and alleviated inflammatory lung injury in mice with lethal endotoxemia. Exp Anim 68: 559-568, 2019.
115. Xiao M, Zhu T, Zhang W, Wang T, Shen YC, Wan QF and Wen FQ: Emodin ameliorates LPS-induced acute lung injury, involving the inactivation of NF-κB in mice. Int J Mol Sci 15: 19355-19368, 2014.
116. Liu Y, Shang L, Zhou J, Pan G, Zhou F and Yang S: Emodin attenuates LPS-induced acute lung injury by inhibiting NLRP3 Inflammasome-dependent pyroptosis signaling pathway in vitro and in vivo. Inflammation 45: 753-767, 2022.
117. Zhang B, Zhai M, Li B, Liu Z, Li K, Jiang L, Zhang M, Yi W, Yang J, Yi D, *et al*: Honokiol ameliorates myocardial ischemia/reperfusion injury in type 1 diabetic rats by reducing oxidative stress and apoptosis through activating the SIRT1-NRF2 signaling pathway. Oxid Med Cell Longev 2018: 3159801, 2018.
118. Tang P, Gu JM, Xie ZA, Gu Y, Jie ZW, Huang KM, Wang JY, Fan SW, Jiang XS and Hu ZJ: Honokiol alleviates the degeneration of intervertebral disc via suppressing the activation of Txnip-NLRP3 inflammasome signal pathway. Free Radic Biol Med 120: 368-379, 2018.
119. Liu Y, Zhou J, Luo Y, Li J, Shang L, Zhou F and Yang S: Honokiol alleviates LPS-induced acute lung injury by inhibiting NLRP3 inflammasome-mediated pyroptosis via Nrf2 activation in vitro and in vivo. Chin Med 16: 127, 2021.
120. Cao F, Tian X, Li Z, Lv Y, Han J, Zhuang R, Cheng B, Gong Y, Ying B, Jin S and Gao Y: Suppression of NLRP3 inflammasome by erythropoietin via the EPOR/JAK2/STAT3 pathway contributes to attenuation of acute lung injury in mice. Front Pharmacol 11: 306, 2020.
121. Homsy E, Das S, Consiglio P, Mcatee C, Zachman A, Nagaraja H, Wewers MD, Exline MC, Mallampalli RK and Sarkar A: Circulating Gasdermin-D in critically Ill patients. Crit Care Explor 1: e0039, 2019.
122. Junqueira C, Crespo N, Ranjbar S, de Lacerda LB, Lewandrowski M, Ingber J, Parry B, Ravid S, Clark S, Schrimpf MR, *et al*: FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. Nature 606: 576-584, 2022.
123. Liu Y, Yang H, Zhu F, Ouyang Y and Pan P: Inhibition of STAT3 phosphorylation by colchicine regulates NLRP3 activation to alleviate sepsis-induced acute lung injury. Inflammopharmacology 31: 2007-2021, 2023.
124. Matthay MA, Zhuo H, Sarma A, Alipanah-Lechner N, Hendrickson C, Kornblith LZ, Schreiber M, Zonies D, Khan A, Robinson B, *et al*: Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome: A Double-blind, placebo-controlled, multicenter phase 2b clinical trial (STAT). Am J Respir Crit Care Med 212: 428-439, 2026.
125. Madurka I, Vishnevsky A, Soriano JB, Gans SJ, Ore DJS, Rendon A, Ulrik CS, Bhatnagar S, Krishnamurthy S, Mc Harry K, *et al*: DFV890: A new oral NLRP3 inhibitor-tested in an early phase 2a randomised clinical trial in patients with COVID-19 pneumonia and impaired respiratory function. Infection 51: 641-654, 2023.
126. Morales Castro D, Dresser L, Granton J and Fan E: Pharmacokinetic alterations associated with critical Illness. Clin Pharmacokinet 62: 209-220, 2023.
127. Tang F, Kunder R, Chu T, Hains A, Nguyen A, Mcbride JM, Zhong Y, Santagostino S, Wilson M, Trenchak A, *et al*: First-in-human phase 1 trial evaluating safety, pharmacokinetics, and pharmacodynamics of NLRP3 inflammasome inhibitor, GDC-2394, in healthy volunteers. Clin Transl Sci 16: 1653-1666, 2023.
128. Tantra T, Rahaman T A A, Nandini and Chaudhary S: Therapeutic role of NLRP3 inflammasome inhibitors against Alzheimer's disease. Bioorg Chem 153: 107912, 2024.
129. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, *et al*: Interleukin-1 blockade with high-dose Anakinra in patients with Covid-19, acute respiratory distress syndrome, and hyperinflammation: A retrospective cohort study. Lancet Rheumatol 2: e325-e331, 2020.
130. Cheng KT, Xiong S, Ye Z, Hong Z, Di A, Tsang KM, Gao X, An S, Mittal M, Vogel SM, *et al*: Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. J Clin Invest 127: 4124-4135, 2017.
131. Vlaar APJ, de Bruin S, Busch M, Timmermans SAME, van Zeggeren IE, Koning R, Ter Horst L, Bulle EB, van Baarle FEHP, van de Poll MCG, *et al*: Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): An exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol 2: e764-e773, 2020.
132. Qin H, Lu N, Chen K, Huang Y, Rui Y, Huang L, Gao Q and Hu J: Inhibiting caspase-3/GSDME-mediated pyroptosis ameliorates septic lung injury in mice model. Mol Immunol 172: 96-104, 2024.

133. Jiang R, Xu J, Zhang Y, Zhu X, Liu J and Tan Y: Ligustrazine alleviate acute lung injury through suppressing pyroptosis and apoptosis of alveolar macrophages. Front Pharmacol 12: 680512, 2021.
134. Lu N, Qin H, Meng Z, Yu Y, Gao Q, Cheng Z, Liu C and Hu J: Inhibiting apoptosis and GSDME-mediated pyroptosis attenuates hepatic injury in septic mice. Arch Biochem Biophys 754: 109923, 2024.
135. Rybinski B and Yun K: Addressing intra-tumoral heterogeneity and therapy resistance. Oncotarget 7: 72322-72342, 2016.
136. Toldo S, Bussani R, Nuzzi V, Bonaventura A, Mauro AG, Cannatà A, Pillappa R, Sinagra G, Nana-Sinkam P, Sime P and Abbate A: Inflammasome formation in the lungs of patients with fatal COVID-19. Inflamm Res 70: 7-10, 2021.
137. Batra R, Whalen W, Alvarez-Mulett S, Gomez-Escobar LG, Hoffman KL, Simmons W, Harrington J, Chetnik K, Buyukozkan M and Benedetti E, et al: Multi-omic comparative analysis of COVID-19 and bacterial sepsis-induced ARDS. PLoS Pathog 18: e1010819, 2022.
138. Vlaar APJ, Witzenrath M, van Paassen P, Heunks LMA, Mourvillier B, de Bruin S, Lim EHT, Brouwer MC, Tuinman PR, Saraiva JFK, *et al*: Anti-C5a antibody (vilobelimab) therapy for critically ill, invasively mechanically ventilated patients with COVID-19 (PANAMO): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med 10: 1137-1146, 2022.
139. van Amstel RBE, Slim MA, Lim EHT, Rückinger S, Seymour CW, Burnett BP, Bos LDJ, van Vught LA, Riedemann NC, van de Beek D, *et al*: Heterogeneity of treatment effect of vilobelimab in Covid-19: A secondary analysis of a randomised controlled trial. Crit Care 28: 210, 2024.
140. Gu W, Zeng Q, Wang X, Jasem H and Ma L: Acute lung injury and the NLRP3 inflammasome. J Inflamm Res 17: 3801-3813, 2024.
141. Bode C, Weis S, Sauer A, Wendel-Garcia P and David S: Targeting the host response in sepsis: Current approaches and future evidence. Crit Care 27: 478, 2023.
142. Vigneron C, Py BF, Monneret G and Venet F: The double sides of NLRP3 inflammasome activation in sepsis. Clin Sci (Lond) 137: 333-351, 2023.
143. Zou K, Wang N, Wang L, Zhu Z, Gu M and Zhang J: Regulated cell death in sepsis-associated liver injury: Molecular mechanisms and therapeutic implications. Front Immunol 17: 1740461, 2026.
144. Heijnen NFL, Hagens LA, Smit MR, Cremer OL, Ong DSY, van der Poll T, van Vught LA, Scicluna BP, Schnabel RM, van der Horst ICC, *et al*: Biological subphenotypes of acute respiratory distress syndrome show prognostic enrichment in mechanically ventilated patients without acute respiratory distress syndrome. Am J Respir Crit Care Med 203: 1503-1511, 2021.
145. Sinha P and Calfee CS: Phenotypes in acute respiratory distress syndrome: Moving towards precision medicine. Curr Opin Crit Care 25: 12-20, 2019.
146. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F and Shao F: Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 526: 660-665, 2015.
147. Broz P: Pyroptosis: Molecular mechanisms and roles in disease. Cell Res 35: 334-344, 2025.
148. Hotchkiss RS, Monneret G and Payen D: Sepsis-induced immunosuppression: From cellular dysfunctions to immunotherapy. Nat Rev Immunol 13: 862-874, 2013.
149. Wu W, Lan W, Jiao X, Wang K, Deng Y, Chen R, Zeng R and Li J: Pyroptosis in sepsis-associated acute kidney injury: Mechanisms and therapeutic perspectives. Crit Care 29: 168, 2025.
150. Zhu L, Hu M, Xu H, Xu H, Ren B, Xu R, Guo M, Chen H, Zhang D and Fang H: The key players of inflammasomes and pyroptosis in Sepsis-induced pathogenesis and organ dysfunction. Front Pharmacol 16: 1586364, 2025.
151. Wang L, Lei W, Zhang S and Yao L: MCC950, a NLRP3 inhibitor, ameliorates lipopolysaccharide-induced lung inflammation in mice. Bioorg Med Chem 30: 115954, 2021.
152. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA and Nhlbi AN: Subphenotypes in acute respiratory distress syndrome: Latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2: 611-620, 2014.
153. Nandi M, Jackson SK, Macrae D, Shankar-Hari M, Tremoleda JL and Lilley E: Rethinking animal models of Sepsis-working towards improved clinical translation whilst integrating the 3Rs. Clin Sci (Lond) 134: 1715-1734, 2020.
154. Peukert K, Fox M, Schulz S, Feuerborn C, Frede S, Putensen C, Wrigge H, Kümmerer BM, David S, Seeliger B, *et al*: Inhibition of Caspase-1 with tetracycline ameliorates acute lung injury. Am J Respir Crit Care Med 204: 53-63, 2021.
155. Fan Y, Mei J, Shen Y, Gao Y, Zhao L, Meng S, Zhou S, Qian Y, Zhang Y, Wang Z, *et al*: Promotion of NLRP3 autophagosome degradation by PV-K nanodevice for protection against macrophage pyroptosis-mediated lung injury. J Nanobiotechnology 23: 148, 2025.
156. Taabazuing CY, Okondo MC and Bachovchin DA: Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. Cell Chem Biol 24: 507-514, 2017.
157. Zhang P, Xu C, Xu L, Wu JJ and Wang L: Pyroptosis-related genes as prognostic biomarkers and immune infiltration features in Sepsis-Induced ARDS: A Single-cell and bulk RNA-Sequencing analysis. J Inflamm Res 18: 14261-14282, 2025.
158. Zhang L, Chen D, Song D, Liu X, Zhang Y, Xu X and Wang X: Clinical and translational values of spatial transcriptomics. Signal Transduct Target Ther 7: 111, 2022.
159. Gong T, Zhang X, Liu X, Ye Y, Tian Z, Yin S, Zhang M, Tang J and Liu Y: Exosomal tenascin-C primes macrophage pyroptosis amplifying aberrant inflammation during sepsis-induced acute lung injury. Transl Res 270: 66-80, 2024.
160. Gong T, Fu Y, Wang Q, Loughran PA, Li Y, Billiar TR, Wen Z, Liu Y and Fan J: Decoding the multiple functions of ZBP1 in the mechanism of sepsis-induced acute lung injury. Commun Biol 7: 1361, 2024.
161. Liu B, Wang Z, He R, Xiong R, Li G, Zhang L, Fu T, Li C, Li N and Geng Q: Buformin alleviates sepsis-induced acute lung injury via inhibiting NLRP3-mediated pyroptosis through an AMPK-dependent pathway. Clin Sci (Lond) 136: 273-289, 2022.
162. Liu Y, Zhang Y, You G, Zheng D, He Z, Guo W, Antonina K, Shukhrat Z, Ding B, Zan J and Zhang Z: Tangeretin attenuates acute lung injury in septic mice by inhibiting ROS-mediated NLRP3 inflammasome activation via regulating PLK1/AMPK/DRP1 signaling axis. Inflamm Res 73: 47-63, 2024.
163. Ning L, Wei W, Wenyang J, Rui X and Qing G: Cytosolic DNA-STING-NLRP3 axis is involved in murine acute lung injury induced by lipopolysaccharide. Clin Transl Med 10: e228, 2020.
164. Suzuki S, Imamura M, Mouri M, Tsuchida T, Tomita H, Matsuoka S, Takita M, Kakinuma K, Kawasaki T, Sakurai K, *et al*: Serum gasdermin D levels are associated with the chest computed tomography findings and severity of COVID-19. Respir Investig 60: 750-761, 2022.
165. Zhao J, Wang H, Zhang J, Ou F, Wang J, Liu T and Wu J: Disulfiram alleviates acute lung injury and related intestinal mucosal barrier impairment by targeting GSDMD-dependent pyroptosis. J Inflamm (Lond) 19: 17, 2022.
166. Yu X, Song Y, Dong T, Ouyang W, Shao L, Quan C, Lee KE, Tan T, Tsung A, Kurabayashi K, *et al*: Loss of PADI2 and PADI4 Ameliorates sepsis-induced acute lung injury by suppressing NLRP3+ macrophages. JCI Insight 9: e181686, 2024.
167. Pan Q, Liu P and Wan M: 6-Gingerol attenuates sepsis-induced acute lung injury by suppressing NLRP3 inflammasome through Nrf2 activation. Folia Histochem Cytobiol 61: 68-80, 2023.
168. Liu Y, Mu S, Li X, Liang Y, Wang L and Ma X: Unfractionated heparin alleviates Sepsis-induced acute lung injury by protecting tight junctions. J Surg Res 238: 175-185, 2019.
169. Wang R, Wang Y, Hu L, Lu Z and Wang X: Inhibition of complement C5a receptor protects lung cells and tissues against lipopolysaccharide-induced injury via blocking pyroptosis. Aging (Albany NY) 13: 8588-8598, 2021.
170. Li X: Polymeric immunoglobulin receptor promotes lung injury in sepsis through caspase-11 mediated pyroptosis. In: Henan University, 2023.
171. Zhao Y, Li K, Wang L, Kuang G, Xie K and Lin S: Dexmedetomidine mitigates acute lung injury by enhancing M2 macrophage polarization and inhibiting RAGE/Caspase-11-Mediated pyroptosis. Front Biosci (Landmark Ed) 29: 409, 2024.
172. Zhang ZT, Zhang DY, Xie K, Wang CJ and Xu F: Luteolin activates Tregs to promote IL-10 expression and alleviating caspase-11-dependent pyroptosis in sepsis-induced lung injury. Int Immunopharmacol 99: 107914, 2021.
173. Peng W, Qi H, Zhu W, Tong L, Rouzi A, Wu Y, Han L, He L, Yan Y, Pan T, *et al*: Lianhua Qingke ameliorates lipopolysaccharide-induced lung injury by inhibiting neutrophil extracellular traps formation and pyroptosis. Pulm Circ 13: e12295, 2023.

174. Hu X, Zou M, Zheng W, Zhu M, Hou Q, Gao H, Zhang X, Liu Y and Cheng Z: Bhlhe40 deficiency attenuates LPS-induced acute lung injury through preventing macrophage pyroptosis. Respir Res 25: 100, 2024.
175. Xu W, Huang X, Li W, Qian G, Zhou B, Wang X and Wang H: Carbon monoxide ameliorates lipopolysaccharide-induced acute lung injury via inhibition of alveolar macrophage pyroptosis. Exp Anim 72: 77-87, 2023.
176. Xie K, Chen YQ, Chai YS, Lin SH, Wang CJ and Xu F: HMGB1 suppress the expression of IL-35 by regulating Naïve CD4+ T cell differentiation and aggravating Caspase-11-dependent pyroptosis in acute lung injury. Int Immunopharmacol 91: 107295, 2021.
177. Wang L, Shen J, Liu W, Li W, Tang W, Zha B, Wu H, Liu X and Shen Q: Abscisic acid for acute respiratory distress syndrome therapy by suppressing alveolar macrophage pyroptosis via upregulating acyloxyacyl hydrolase expression. Eur J Pharmacol 977: 176672, 2024.
178. Zhang ML, Wang M, Chen J, Liu YJ, Yu YJ, Liu LM, Zheng XH, Xiao YC, Zhang JM, Zhu MX, *et al*: Isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxypropanoate protects lipopolysaccharide-induced acute lung injury in mice by attenuating pyroptosis. Eur J Pharmacol 942: 175545, 2023.
179. Changliang H, Yan W, Ling L and Jian L: Human umbilical cord-derived mesenchymal stem cells thwart pyroptosis of lung tissue cells in septic mice. Chin J Tissue Eng Res 29: 6642-6648, 2025.
180. Xueying X: MANF improves acute lung injury by inhibiting the PRDX6-ROS-GSDMD pathway. In: Anhui Medical University, 2023.
181. Li X, Jamal M, Guo P, Jin Z, Zheng F, Song X, Zhan J and Wu H: Irisin alleviates pulmonary epithelial barrier dysfunction in sepsis-induced acute lung injury via activation of AMPK/SIRT1 pathways. Biomed Pharmacother 118: 109363, 2019.
182. Xia W, Pan Z, Zhang H, Zhou Q and Liu Y: ERRα protects against sepsis-induced acute lung injury in rats. Mol Med 29: 76, 2023.
183. Wang Y, Deng F, Zhong X, Du Y, Fan X, Su H and Pan T: Dulaglutide provides protection against Sepsis-induced lung injury in mice by inhibiting inflammation and apoptosis. Eur J Pharmacol 949: 175730, 2023.
184. Liu S, Gao S, Yang Z and Zhang P: miR-128-3p reduced acute lung injury induced by sepsis via targeting PEL12. Open Med (Wars) 16: 1109-1120, 2021.
185. Wang Y, Wang X, Zhang L and Zhang R: Alleviation of acute lung injury in rats with sepsis by resveratrol via the phosphatidylinositol 3-Kinase/Nuclear Factor-Erythroid 2 related factor 2/Heme Oxygenase-1 (PI3K/Nrf2/HO-1) pathway. Med Sci Monit 24: 3604-3611, 2018.
186. Song J, Zhang J, Shi J, Pan X and Mo D: Breviscapine reduces Sepsis-induced acute lung injury by targeting CASP8 to regulate neutrophil apoptosis and inflammation. J Inflamm Res 17: 5161-5176, 2024.
187. Zhang JR, Lin Q, Liang FQ and Xie T: Dexmedetomidine attenuates lung injury by promoting mitochondrial fission and oxygen consumption. Med Sci Monit 25: 1848-1856, 2019.
188. Zhang M, Xu G, Zhou X, Luo M, Ma N, Wang X, Wang Z, Tang H, Wang X, Li Y, *et al*: Mesenchymal stem cells ameliorate H9N2-induced acute lung injury by inhibiting caspase-3-GSDME-mediated pyroptosis of lung alveolar epithelial cells. Eur J Pharmacol 960: 176148, 2023.
189. Huang J, Ren K and Huang L: Coptisine attenuates sepsis lung injury by suppressing LPS-induced lung epithelial cell inflammation and apoptosis. Allergol Immunopathol (Madr) 51: 30-36, 2023.
190. Zhang E, Wang J, Chen Q, Wang Z, Li D, Jiang N and Ju X: Artesunate ameliorates sepsis-induced acute lung injury by activating the mTOR/AKT/PI3K axis. Gene 759: 144969, 2020.
191. Zhong K, Huang Y, Chen R, Pan Q, Li J and Xi X: The protective effect of ginsenoside Rg1 against sepsis-induced lung injury through PI3K-Akt pathway: Insights from molecular dynamics simulation and experimental validation. Sci Rep 14: 16071, 2024.
192. Xiao Z, Long J, Zhang J, Qiu Z, Zhang C, Liu H, Liu X, Wang K, Tang Y, Chen L, *et al*: Administration of protopine prevents mitophagy and acute lung injury in sepsis. Front Pharmacol 14: 1104185, 2023.
193. Yang R, Yang H, Wei J, Li W, Yue F, Song Y, He X and Hu K: Mechanisms underlying the effects of Lianhua Qingwen on sepsis-induced acute lung injury: A network pharmacology approach. Front Pharmacol 12: 717652, 2021.
194. Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, Rogers AJ, Gotts JE, Wiener-Kronish JP, Bajwa EK, *et al*: Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): A randomised phase 2a safety trial. Lancet Respir Med 7: 154-162, 2019.
195. Wilson JG, Liu KD, Zhuo H, Caballero L, Mcmillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee J, *et al*: Mesenchymal stem (stromal) cells for treatment of ARDS: A phase 1 clinical trial. Lancet Respir Med 3: 24-32, 2015.
196. Mcelvaney OJ, Mcevoy NL, Boland F, Mcelvaney OF, Hogan G, Donnelly K, Friel O, Browne E, Fraughen DD, Murphy MP, *et al*: A randomized, double-blind, placebo-controlled trial of intravenous alpha-1 antitrypsin for ARDS secondary to COVID-19. Med 3: 233-248, 2022.
197. Chanchalani G: Aviptadil in acute respiratory distress syndrome-promise or mirage? Indian J Crit Care Med 29: 895-896, 2025.

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