Unraveling the synergy of inflammation and apoptosis in sepsis-induced acute lung injury: Insights and therapeutic perspectives (Review)

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Abstract. Sepsis refers to the state of the body exhibited after an uncontrolled reaction to infection. This is marked by the impaired function of multiple organs, with the lungs often being impacted. Individuals affected by sepsis often suffer acute lung injury, which may advance to a more serious acute respiratory distress syndrome. Inflammatory responses and apoptosis are key in the onset and progression of sepsis-induced acute lung injury (SALI). The present review examines the pathogenesis of SALI, emphasizing the synergistic roles of inflammatory responses and apoptosis as well as their effect on lung tissue. An overactivated inflammatory response can exacerbate lung tissue damage and promote the occurrence of apoptosis. Meanwhile, excessive apoptosis can further intensify the inflammatory response, therefore resulting in a vicious cycle. The present review also discusses therapeutic strategies that target the synergistic effects of inflammation and apoptosis, including NF-κB pathway inhibitors, MAPK signaling pathway inhibitors, antioxidants, mesenchymal stem cell therapy and biologics. Despite the progress made to date in understanding the synergistic effects of inflammation and apoptosis, there are still numerous areas that require further exploration, such as the complex molecular regulatory networks connecting inflammation and apoptosis as well as the impact of clinical individual differences on this synergy, which require further investigation to ultimately translate mechanistic findings into targeted therapies, thus providing new insights and approaches for the treatment of SALI.

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1. Introduction

Sepsis represents a serious medical condition marked by the sudden failure of multiple organ systems due to an inappropriate response to infection by the host (1). Sepsis has become one of the primary contributors to severe illness and mortality worldwide (2). Based on a 2020 research report involving the Intensive Care Units (ICUs) of 44 hospitals nationwide, the Chinese Expert Consensus on Early Prevention and Blockade of Sepsis in Emergency Medicine indicated that the incidence rate in ICUs was 20.6%, with a 90-day mortality rate of 35.5% (3). Notably, nearly 60% of these patients experience co-infection of the lungs (4), indicating that the lungs may be the most susceptible and severely affected organ in sepsis. Acute lung injury (ALI) impacts 25-50% of patients suffering from sepsis and, if not treated promptly and effectively, can progress to acute respiratory distress syndrome (ARDS), a more severe condition (5). Effective sepsis-induced acute lung injury (SALI) therapies remain limited, prompting urgent translational research. The pathological characteristics of ALI involve extensive inflammation resulting in harm to alveolar epithelial cells (AECs), breakdown of the pulmonary vascular endothelial barrier and subsequent accumulation of protein-rich inflammatory edema fluid within the alveolar spaces, ultimately causing diffuse alveolar damage (6). Apoptosis and necrosis directly contribute to epithelial and endothelial cell damage in sepsis, as demonstrated

Jiang *et al* (7). Consequently, modulating apoptosis and alleviating lung inflammation are promising therapeutic strategies for managing ALI.

The inflammatory response serves as the body's defense mechanism against various stimuli, including infections, pathogenic microorganisms, trauma and metaplasia. In the context of sepsis-induced ALI, this response is primarily triggered by the activation of lung macrophages and the infiltration of neutrophils. The overactive engagement of these immune cells leads to the increased release of pro-inflammatory substances, which further exacerbates inflammation and ultimately causes tissue injury. Apoptosis, often known as programmed cell death, is a genetically controlled mechanism of systematic and self-directed cell death that removes damaged, older or excess cells. During infection, apoptosis serves a key role in limiting pathogen replication, preventing the spread of infection and maintaining tissue homeostasis (8). However, dysregulated apoptosis and excessive apoptotic activity may also contribute to the pathogenesis of ALI.

The present review examines the combined influence of apoptosis and inflammation in SALI to offer a thorough theoretical foundation for a deeper understanding of the mechanisms underlying this condition.

2. Activation and regulation of the inflammatory response of ALI in sepsis

Recruitment and activation of inflammatory cells

Mechanisms of neutrophil infiltration in lung tissue. Neutrophils serve as essential elements of the innate immune system, contributing to the defense against pathogens that invade the body. During sepsis, neutrophils become activated and are released into the circulation in large numbers, where they accumulate in endothelial cells (ECs) at the site of infection (9,10). Intercellular cell adhesion molecules (ICAMs) are upregulated under inflammatory conditions through pro-inflammatory signaling, facilitating the migration of neutrophils to lung tissue and their firm adhesion to ECs. A previous study has demonstrated that ICAM-1 levels in lung capillary cells are markedly elevated within 24 h of the onset of infection (11). P-selectin on ECs further mediates neutrophil aggregation and rolling adhesion, resulting in substantial neutrophil accumulation in the pulmonary microcirculation and excessive adhesion to the endothelium. This aberrant alteration contributes to the activation of pro-inflammatory chemokines [including IL-1, TNF-α and lipopolysaccharide (LPS)], which further recruit neutrophils to infected tissues.

Within neutrophils, phagosomes fuse with lysosomes to form phagolysosomes, which are key in the defense against invading pathogens. However, during phagocytosis, the contents of neutrophil granules may be released into the extracellular environment, particularly hydrolytic enzymes released by lysosomes. This leakage can lead to local tissue damage and amplify acute inflammatory signals, ultimately exacerbating inflammatory lung injury (12). Additionally, neutrophils can traverse the alveolar epithelium into the lumen and adhere to the epithelial surface using β2-integrins. In the inflammatory state, the migration of numerous neutrophils results in increased alveolar epithelial permeability. Neutrophils that have been activated secrete various cytokines, such as proteases, reactive oxygen species (ROS), pro-inflammatory molecules and agents that facilitate coagulation. Additionally, these harmful mediators undermine the structural integrity of the tight junctions (TJs) located between the epithelial cells.

In the context of sepsis, neutrophils migrate from the intravascular space to inflamed tissues through the transendothelial migration (TEM) cascade. Previous research indicates that, during inflammation, the levels of ECs and extracellular vesicles (EVs) in human blood notably increase (13). EC-derived EVs facilitate the reverse TEM (rTEM) of neutrophils from tissues back into the vasculature. Neutrophils returning to the circulatory system through rTEM can carry inflammatory signals and pathogen components acquired from local tissues, thereby promoting the spread of inflammation to distant organs and exacerbating distal lung injury. Zi *et al* (10) demonstrated that the proportion of rTEM neutrophils in the peripheral blood of patients with sepsis was elevated, particularly in those who developed ARDS.

A previous study found that activated neutrophils can recruit and degrade pathogens by producing neutrophil extracellular traps (NETs) (14). NETs are primarily composed of nuclear DNA, histones, antimicrobial peptides and enzymes such as myeloperoxidase (MPO) and elastase. The process by which neutrophils form NETs is known as NETosis, a novel form of programmed neutrophil death. In previous years, increasing researchs have demonstrated that NETosis is closely associated with sepsis-induced lung injury and exhibits a complex dual role (15,16). On the one hand, in the early stages of sepsis, NETs can help clear pathogens and limit their spread by capturing and killing bacteria. However, excessive NETosis can lead to lung tissue damage. Pathogen-associated molecular patterns such as LPS, induce neutrophils to release NETs by activating toll-like receptor 4 (TLR4). Meanwhile, MPO and hydrogen peroxide (H_2O_2) produced by NETs can further activate the NF-κB signaling pathway through the TLR signaling pathway of epithelial cells, thereby enhancing the pro-inflammatory response of ECs, upregulating the expression of adhesion molecules such as ICAM-1 and vascular cell adhesion molecule 1 and promoting the secretion of pro-inflammatory factors, leading to EC damage (17). Furthermore, the histones in NETs can directly cause lung epithelial cell and EC death due to their cytotoxicity, thereby compromising the integrity of cell membranes. Consequently, histone levels can serve as a clinical marker for the severity of sepsis-induced lung injury. On the other hand, the DNA in NETs is associated with coagulation, providing a scaffold for platelet binding and stimulating platelet aggregation, activating the extrinsic coagulation pathway, promoting microthrombus formation and leading to pulmonary microcirculation disorders and ventilation/perfusion mismatch, thereby exacerbating lung injury (18).

Functional shifts in macrophages and inflammatory amplification. Macrophages represent a highly heterogeneous class of immune cells that serve a pivotal role in the body's immune system. Macrophages can polarize into different phenotypes depending on stimuli from various tissue microenvironments. The primary phenotypes are inflammatory or classically activated macrophages (M1) and alternatively activated macrophages (M2) that promote healing. In response to inflammatory stimuli, the actions of LPS or interferon, whether

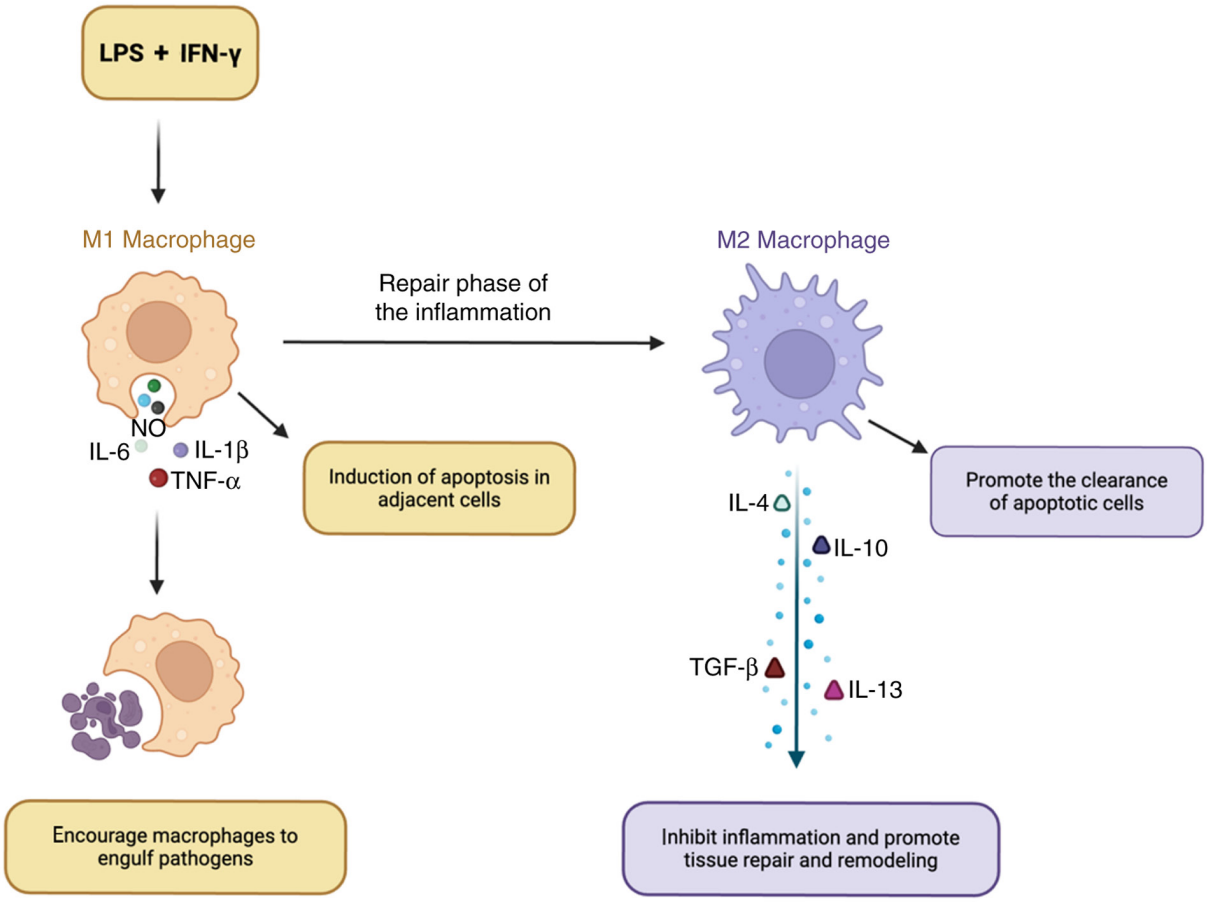

Figure 1. Functional shifts in macrophages. LPS or IFN promotes the polarization of macrophages toward the M1 phenotype, resulting in an increased release of pro-inflammatory factors such as TNF-α, NO, IL-1β and IL-6. In the later stages of inflammatory repair, M1 macrophages transition into M2 macrophages, which secrete anti-inflammatory factors such as IL-4, IL-10, IL-13 and TGF-β, thereby suppressing the inflammatory response and facilitating tissue repair and remodeling. LPS, lipopolysaccharide; NO, nitric oxide.

alone or synergistically, promote macrophage polarization towards the M1 phenotype, thereby increasing the release of pro-inflammatory factors [such as TNF-α, nitric oxide (NO), IL-1β and IL-6], which are essential for pathogen elimination and defense (19). During the repair phase of late inflammation, M1 macrophages polarize toward M2 macrophages, secreting anti-inflammatory factors (including IL-4, IL-10, IL-13 and TGF-β) to inhibit the inflammatory response and facilitate tissue repair and remodeling (Fig. 1). Dang *et al* (20) noted that macrophage polarization within the lungs has a notable influence on the onset of, and recovery from, septic lung injuries. An imbalance in the shift between M1 and M2 macrophages, which leads to ongoing production of pro-inflammatory mediators, can result in tissue harm. It has previously been reported that, in cases of SALI, M1 macrophages exacerbate lung damage due to unchecked inflammatory responses (21). Additionally, Li *et al* (22) demonstrated that in Traditional Chinese Medicine (TCM), the compound Lianhua Qingdian effectively alleviates SALI by enhancing the infiltration of M2 macrophages. This mechanism may involve promoting the transformation of macrophages from the M1 to the M2 phenotype by activating the peroxisome proliferator-activated receptor γ signaling pathway, inhibiting the NF-κB signaling pathway and alleviating inflammatory responses. However, it is important to note that these results were obtained from a mouse model of LPS-induced ALI and there is still an overall lack of supporting clinical data in humans.

M2 macrophages possess anti-inflammatory and tissue repair properties, thus serving a key role in the recovery process of patients with ARDS. Yang *et al* (23) found that, in LPS-induced ARDS mouse models, the M2/M1 alveolar macrophage ratio notably decreased as the severity of lung injury increased. Conversely, the intratracheal administration of exogenous M2 alveolar macrophage-derived EVs markedly improved LPS-induced ARDS yet reduced the levels of inflammatory factors in bronchoalveolar lavage fluid. Similarly, in patients with ARDS who underwent continuous mechanical ventilation or succumbed to disease within 28 days, there was found to be a persistent M1 phenotype and insufficient M2 transformation (24). It may be inferred that the anti-inflammatory and pro-repair effects mediated by M2 macrophages are key for alveolar epithelial cell reconstruction and pulmonary function recovery in patients with ARDS during the recovery phase.

Release of inflammatory mediators and signaling pathways

Formation and role of cytokine networks. Cytokines are a class of small proteins with diverse biological activities. During inflammation, these cytokines can activate immune cells to synthesize and secrete pro-inflammatory factors,

with the overproduction of TNF-α, IL-1β and IL-6 being characteristic of systemic inflammatory response syndrome. Excessive release of cytokines leads to mutual stimulation among other different cytokines, forming a complex network. These cytokines bind to target cells through cell surface receptors, activating signal transduction pathways and initiating a series of inflammatory cascade responses, with NF-κB having been identified as a key target (25). In healthy cells, NF-κB resides in the cytoplasm, forming a complex with IκB that then inhibits further NF-κB activity. Upon stimulation by cytokines, IκB undergoes phosphorylation through the activation of the inhibitor of κB kinase, followed by its ubiquitination and degradation. This sequence of events leads to the relocation of NF-κB into the nucleus. Consequently, this mechanism enhances the expression of pro-inflammatory cytokines, including IL-6, IL-1β and TNF-α, thereby intensifying the inflammatory responses.

Synergistic effects of chemokines and lipid mediators. Chemokines are a class of small molecular weight cytokines produced by leukocytes in response to external stimuli. During the inflammatory response, chemokines facilitate the migration of circulating leukocytes to injured tissues by recruiting and activating immune cells, thereby forming a concentration gradient, which is further established by the binding of chemokines to glycosaminoglycans in the extracellular matrix and endothelium (26). Neutrophils tend to be the first immune cells to reach the site of infection, where they serve a key role in engulfing pathogens and clearing cellular debris through phagocytosis. Subsequently, monocytes migrate to the infection, where they transform into macrophages, continuing the fight against pathogens while releasing various cytokines, including TNF-α, IL-1β, IL-6, prostaglandins and leukotrienes. The chemokine family is generally divided into four categories: Two primary subfamilies (CXC and CC) and two secondary subfamilies (CX3C and C). The distinct chemokine groups interact with specific receptors found on various cell types and are coordinated with the adhesion molecules present, thus contributing to the inflammatory response (27).

Chemokine receptors are part of the heptameric transmembrane guanosine triphosphate-binding G protein-coupled receptor superfamily, which trigger an intracellular signaling cascade through the associated trimeric G proteins. This mechanism promotes the adhesion of target cells to the endothelial lining and directs their migration toward the infection site (28). Among these, monocyte chemoattractant protein 1 (MCP-1) (29), also known as CC chemokine ligand 2, is classified within the CC subfamily of chemokines. In the early stages of inflammation, MCP-1 attaches to the CC motif chemokine receptor 2 receptor, stimulating the accumulation of monocytes and their transformation into macrophages (30). MCP-1 serves a key role in directing the appropriate immune response associated with infection and inflammation (31). A different category of CXC chemokines, such as macrophage inflammatory protein 2 [also referred to as C-X-C motif chemokine ligand (CXCL) 2] and CXCL8 (often called IL-8), are able to promote the infiltration of innate immune cells and work in conjunction with lipid signaling. Additionally, prostaglandin E2 (PGE2) and leukotriene B4, produced by ω-6 polyunsaturated fatty acid, serve as pro-inflammatory lipid mediators that activate inflammatory vesicles and initiate the endoplasmic reticulum (ER) stress response (32). These processes serve a key role in the onset, progression and resolution of inflammation.

3. Triggering and regulation of apoptosis in ALI in sepsis

Activation of apoptosis-related signaling pathways

Death receptor-mediated apoptosis pathway. Death receptor pathways involve specific proteins on cell membranes binding to ligands that carry apoptotic signals, subsequently transducing these signals into the cell and ultimately inducing apoptosis. The activation of the death receptor pathway mainly occurs through death receptors located on the cell surface, including the Fas cell surface and TNF receptors. These receptors initiate the apoptotic process by recruiting junctional proteins, including Fas-associated via death domain and promoting cysteine aspartyl proteases, such as caspase-8, upon binding with specific death ligands such as Fas ligands and TNF-α. Subsequently, caspase-8 activates downstream effector enzymes, including caspase-3 and caspase-7, ultimately leading to apoptosis (Fig. 2).

Caspases, which are cysteine-specific cysteine proteases, serve a pivotal role in the regulation of apoptosis. Caspases can be categorized into two groups: i) Initiating caspases (including caspases-2, -8, -9 and -10); and ii) executioner caspases (including caspases-3, -6 and -7) (33). When an initiating caspase becomes activated, it processes and triggers the downstream executioner caspases, which subsequently cleave cellular proteins at particular aspartate residues, thus facilitating the process of apoptosis (34). These executioner caspases are key in shaping the distinctive characteristics of apoptotic cells by cleaving a multitude of cellular proteins (including, but not limited to, caspase-activated inhibitor of DNase, aggrecan and Pac21), ultimately resulting in DNA fragmentation. This cascade of events leads to observable apoptotic traits such as nuclear condensation, shrinkage of the cell and blistering of the membrane. Generally, caspase enzymes are synthesized as inactive zymogens and their activation pathways include both exogenous and endogenous mechanisms, with the death receptor pathway being classified as exogenous (35).

In the exogenous pathway, caspase-8 not only activates the execution of caspases, but also facilitates the cleavage of BH3 interacting domain death agonist (Bid), leading to its translocation to the mitochondria (25). The CD95 signaling model proposed by Algeciras-Schimnich *et al* (36) suggests that the involvement of the mitochondrial pathway in apoptosis is determined through a dual-threshold mechanism. As a death receptor, CD95, upon binding with its ligand, induces the formation of the death-inducing signaling complex (DISC), the efficiency of which directly determines the levels of caspase-8 produced. However, there are notable differences in DISC formation between types I and II cells. In type I cells, DISC formation is highly efficient and stable, further generating a substantial quantity of caspase-8 that exceeds the higher threshold, directly activating caspase-3 to trigger apoptosis. In type II cells, the formation of DISC is inefficient and unstable, resulting in only a minimal quantity of caspase-8 that only just exceeds the lower threshold. Apoptosis initiation can only be triggered by amplifying the cell death signal through the mitochondrial pathway through the cleavage of Bid (36).

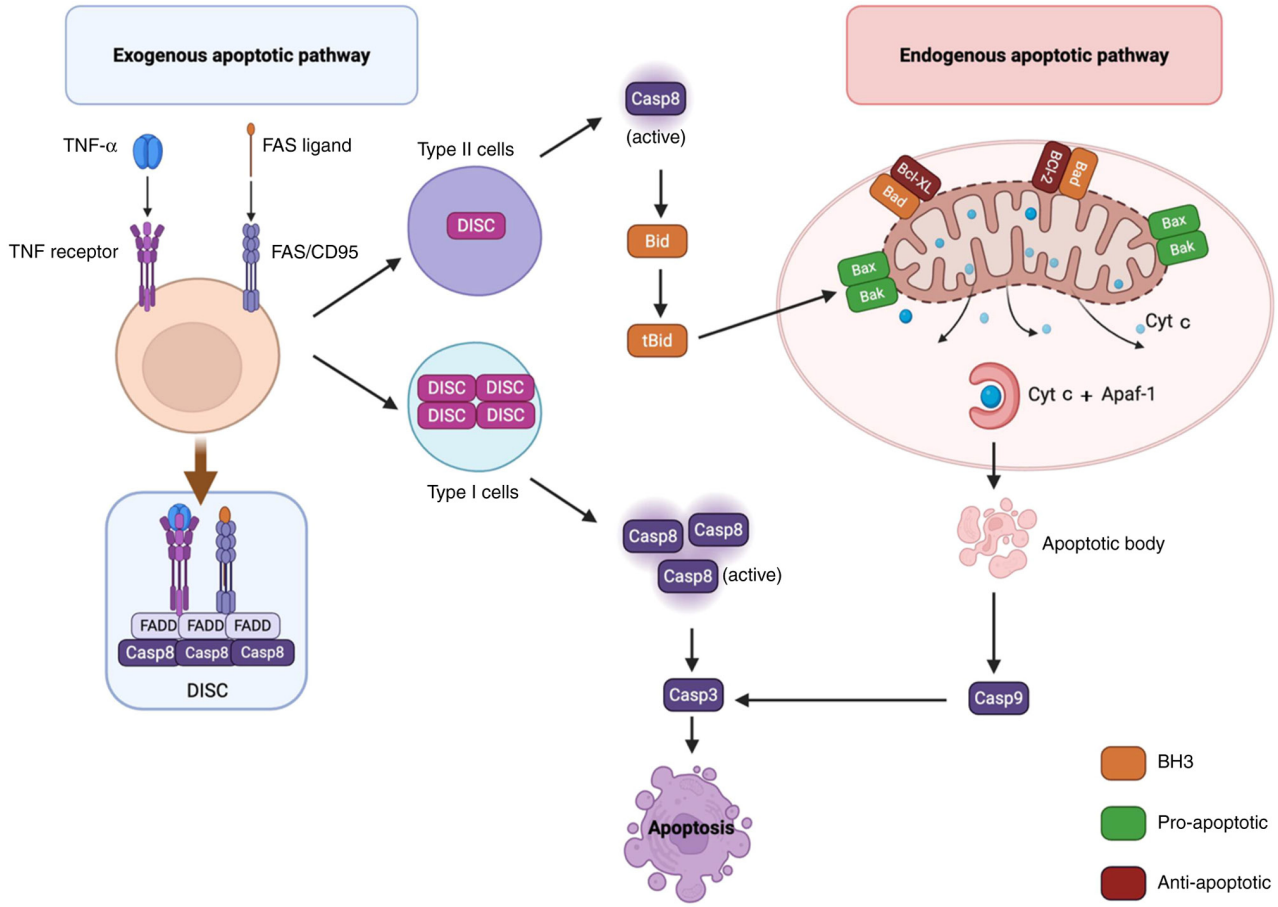

Figure 2. Activation of apoptosis-related signalling pathways. The activation of the extrinsic apoptotic pathway is primarily mediated by the binding of specific ligands to the Fas receptor and TNF receptor on the cell surface, which is followed by the recruitment of FADD to form the DISC. Notably, there are marked differences in the formation of DISC between type I and II cells. In type I cells, the DISC is formed efficiently and stably, resulting in the production of a substantial amount of Casp8. This enzyme directly activates downstream effector enzymes, including Casp3, thereby triggering apoptosis. Conversely, in type II cells, DISC formation is inefficient and unstable, yielding only a limited amount of Casp8, which subsequently cleaves Bid into tBid. tBid then translocates to the outer mitochondrial membrane, activating Bax/Bak, which leads to the disruption of mitochondrial membrane integrity, the release of Cyt c and subsequent binding with Apaf-1 to form the apoptosome. This process further activates Casp9, which triggers downstream Casp3 to initiate apoptosis. DISC, death-inducing signaling complex; Bid, BH3 interacting domain death agonist; tBid, truncated Bid; Bak, Bcl-2 homologous antagonist killer; Cyt c, cytochrome c; Apaf-1, apoptotic protease activating factor 1; FADD, Fas-associated death domain; Casp, caspase; Bad, Bcl-2-associtaed death protein.

Consequently, the process of apoptosis requires participation from the mitochondrial apoptotic pathway, wherein Bid acts as a key connection between the death receptor and mitochondrial apoptotic pathways.

Initiation of the mitochondrial apoptotic pathway. The mitochondrial apoptotic pathway is endogenous. When triggered by factors such as DNA damage, metabolic stress, ER stress or growth factor deprivation, the integrity of the mitochondrial membrane is disrupted (37,38). Increased mitochondrial membrane permeability leads to the release of cytochrome c (Cyt c) from the mitochondria into the cytoplasm. Cyt c interacts with apoptosis-activating factor 1 to create an ATP-dependent apoptotic complex. This complex activates caspase-9, which subsequently triggers the activation of downstream caspases-3 and -7, consequently initiating a cascade of caspase reactions that leads to apoptosis (Fig. 2). Furthermore, once released from the mitochondria, Cyt c can bind to inositol triphosphate receptors located in the ER. This binding results in an elevation of local calcium levels, which then enhances the release of Cyt c and triggers the initiation of apoptosis (39). Conversely, protein tyrosine phosphatase, which is located between the inner and outer membranes of the mitochondria, can facilitate the creation of the mitochondrial permeability transition pore (MPTP), permitting the movement of molecules of ≤1.5 kDa in size. Abnormal MPTP opening has been found to impair mitochondrial function and promote apoptosis (40).

Mitochondria serve as the primary source of cellular energy and are also the principal site for the production of intracellular ROS. During apoptosis, mitochondrial damage and ROS production exacerbate each other, resulting in a vicious cycle (41). ROS can compromise both the integrity and functionality of the mitochondrial membrane, resulting in the release of apoptotic factors, which in turn, further enhances ROS production, aggravating mitochondrial impairment (42). Wang *et al* (43) induced oxidative stress in Hepa1-6 cells through the application of fluorine (F), which led to increased levels of intracellular ROS and propane-1,2-diol and mitochondrial injury. The oxidative stress induced by F resulted in marked elevations in intracellular ROS, malondialdehyde (MDA) and NO concentrations. Furthermore, there was a notable upregulation in the protein expression of Cyt c,

caspase-9 and caspase-3, along with a considerable increase in apoptotic cell count and extensive mitochondrial vacuolation, as evidenced by transmission electron microscopy. This demonstrated that ROS mediates mitochondrial damage, thereby exacerbating apoptotic injury.

Role of apoptosis-regulating genes and proteins

Imbalance in the regulation of Bcl-2 family proteins. Bcl-2 family proteins are the primary regulators of the release of mitochondria-associated apoptotic factors and can be classified into three primary categories based on their biological functions: i) Anti-apoptotic proteins, such as Bcl-2, Bcl-XL, Bcl-w and myeloid cell leukemia 1 (Mcl-1); ii) pro-apoptotic proteins, such as Bax and Bcl-2 homologous antagonist killer (Bak); and iii) BH3-only proteins, such as Bad, Bid, Bcl-2-interacting mediator of cell death (Bim), phorbol-12-myristate-13-acetate-induced protein 1 and p53 upregulated modulator of apoptosis (Puma). In healthy cells, a balance is sustained between anti-apoptotic and pro-apoptotic proteins. However, in a septic state, the concentration of free Bad in the cytoplasm increases, allowing Bad to bind to Bcl-2 and Bcl-XL. This binding leads to the dissociation of Bax and Bak and the formation of pore-protein complexes through interactions with other Bax or Bak proteins. These complexes can insert into the outer mitochondrial membrane, disrupting its integrity and ultimately resulting in the release of intracellular apoptosis-inducing factors (Cyt c) and triggering apoptosis (44).

Bax is a crucial pro-apoptotic protein. Upon receiving apoptotic signals, Bax, which initially exists as a monomer in the cytosol, translocates to the mitochondrial surface, where it forms trans-mitochondrial membrane pores, resulting in increased membrane permeability and further facilitating the release of apoptotic factors (45). Simultaneously, when the Bcl-2/Bax imbalance disrupts the TJ proteins between alveolar epithelial cells, it directly or indirectly induces the apoptosis of alveolar epithelial cells, leading to the destruction of the alveolar epithelial barrier and increased permeability, which ultimately causes alveolar edema, alveolar collapse and refractory hypoxemia. Previous research has shown that polydeoxyribonucleotide (PDRN) extracted from salmon sperm is able to promote tissue healing and reduce apoptosis and inflammation. An *et al* (46) treated a rat model of LPS-induced lung injury with intraperitoneal injections of PDRN and observed a notable reduction in lung injury scores. In addition, the ratio of the pro-apoptotic protein Bax relative to the anti-apoptotic protein Bcl-2 was reduced, suggesting that PDRN treatment alleviated lung damage through the inhibition of apoptosis.

Regulation of apoptosis by p53. The p53 protein functions as a transcription factor, triggering the expression of various target genes and serving a key role in maintaining genomic stability, regulating the cell cycle, facilitating DNA repair and promoting apoptosis. Under standard physiological circumstances, p53 is targeted for degradation by murine double minute 2 homolog (MDM2) and murine double minute X (MDMX), which ubiquitinate it, thereby keeping its intracellular levels low through proteasomal degradation. By contrast, when cells face stressors such as DNA damage, hypoxia or infection, the process of p53 ubiquitination is suppressed, causing a rapid increase in its cellular concentrations (47). Various sensor proteins, such as the ataxia-telangiectasia-mutated protein, ataxia-telangiectasia and Rad3-related protein, checkpoint kinase 1, checkpoint kinase 2, DNA-dependent protein kinase and the p14ARF protein, become activated and p53 stability is enhanced through post-translational modifications, including acetylation, methylation and phosphorylation. Stabilized p53 proteins form tetramers in the nucleus that bind to p53 response elements on target DNA, thereby regulating gene transcription (48). On one side, p53 is involved in apoptosis mediated by mitochondria through activating the transcription of pro-apoptotic proteins such as Bax, Puma and Bid. Conversely, p53 can trigger apoptosis without relying on transcription. The p53 protein, in a manner that does not depend on its transcriptional functions, translocates to the mitochondria, where it competes with Mcl-1 for binding to Bak through protein interactions, leading to the release of Bak from Mcl-1 and initiates Bak oligomerization (49). Furthermore, p53 interacts with Bcl-XL, prompting the detachment of Bax from the Bax/Bcl-XL complex, subsequently enhancing oligomerization. The oligomerization of Bax and Bak modifies the permeability of the outer mitochondrial membrane, allowing the release of Cyt c into the cytoplasm, which then activates caspase proteases, ultimately prompting apoptosis (50).

In addition, the activation of p53 can lead to the disruption of the EC cytoskeleton, increased vascular permeability and the induction of apoptosis in alveolar type II epithelial cells, severely affecting the synthesis and secretion of pulmonary surfactant (PS). This results in increased alveolar surface tension, alveolar collapse and ventilator-associated lung injury. Previous research has found that MDM2 promotes the degradation of p53 protein through the ubiquitination pathway, maintaining p53 at low levels. When MDM2 function is lost, uncontrolled activation of p53 leads to apoptosis, barrier disruption and amplification of inflammation, ultimately exacerbating lung injury (51).

4. Mechanisms of synergy between inflammation and apoptosis

Induction of apoptosis by inflammatory mediators

Molecular crosstalk of cytokines to apoptotic signaling pathways. When sepsis manifests, there is an enhanced release of pro-inflammatory agents in the body (such as TNF-α, IL-1β and IL-6) and the NF-κB pathway is dysregulated, which exacerbates the inflammatory response or transcriptionally activates the Bcl-2 family, thus inducing apoptosis through an 'inflammatory storm'. Conversely, activation of NF-κB further induces the production of TNF-α and IL-1β, forming a positive feedback loop. Furthermore, elevated levels of activated cytokines such as IL-6 attach to the membrane-associated IL-6 receptor (IL-6R), resulting in the formation of the IL-6/IL-6R complex. This complex then associates with glycoprotein 130 (gp130) to establish a signaling complex that triggers the MAPK cascade through the recruitment of gp130. Similarly, locally released cytokines (such as IL-1β or TNF-α) have been shown to activate MAPK pathways, including JNK and ERK (52,53). Abnormal activation of these signaling pathways further promotes the activation

of inflammatory cells and disrupts the stress response, thus inducing cell apoptosis, ultimately leading to tissue injury.

Inflammation-induced oxidative stress and apoptosis. Oxidative stress influences apoptosis through various pathways. An important component of this process is the action of ROS, which function as 'redox messengers' and are crucial for redox regulation and cellular signaling. Generally, ROS are understood to encompass free radicals derived from oxygen (O_2), including superoxide anion (O_2^-), hydroxyl radical (HO^-), peroxyl radical and alkoxyl radical, along with non-free radical O_2 derivatives such as hydrogen peroxide (H_2O_2). However, ROS, once produced in excess, may lead to oxidative modification of cellular macromolecules, which in turn may cause notable damage to cellular proteins and DNA. Mokrá (54) suggested that oxidative stress is not only an important causative factor in ALI but may also contribute to extensive damage to lung tissues and worsening inflammatory responses through activation of apoptotic pathways.

Mitochondria serve as the primary location for the production of ROS, with 1-2% of the O_2 consumed by mitochondria being utilized for the generation of ROS, particularly during the electron transfer process to O_2 within the electron transport chain. In the presence of inflammation and tissue injury, a marked increase in the release of mitochondrial ROS (mtROS) occurs. This increase may result in mitochondrial membrane depolarization that relies on the pore-forming protein gasdermin D (GSDMD). Consequently, there is a reduction in the mitochondrial membrane potential, prompting GSDMD to associate with the mitochondrial membrane, thereby forming a pore. This process ultimately enhances the permeability of the mitochondrial membrane, facilitates the release of apoptotic factors and triggers the activation of mitochondrial apoptotic pathways. In addition, it has been found that ROS can also inhibit the degradation and transport of mitochondrial proteins, which is the main cause of mitochondrial dysfunction (55). In addition, oxidative stress can trigger the activation of transcription factors such as NF-κB and p53 (56), influencing the expression and functionality of proteins associated with apoptosis (such as Bcl-2). Previous research has demonstrated that, in cells treated with H_2O_2, there is a marked reduction in Bcl-2 protein levels (57), thereby modulating the apoptotic process.

Exacerbation of the inflammatory response by apoptotic cells

Damage-associated molecular patterns (DAMPs) released by apoptotic cells. Alveolar macrophages, as the primary immune cells in the lungs, encounter infections, injuries and stress, leading to the transformation of specific endogenous molecules into DAMPs. These DAMPs can activate the immune system and exhibit pro-inflammatory characteristics. In a steady-state environment, endogenous molecules, including nucleic acids, proteins, ions, glycans and metabolites, usually do not initiate an immune response. However, during stress, these molecules can be transformed into DAMPs through three mechanisms: i) Positional substitution; ii) alterations in properties; or iii) changes in concentration, with positional substitution being the predominant mechanism (58). It is evident that, during infection or stress, the mitochondrial membrane sustains damage, leading to increased membrane permeability and the release of intracellular substances that can induce apoptosis. Proteins or peptides released into the extracellular space by apoptotic cells can be converted into DAMPs such as nuclear proteins like high mobility group box 1 (HMGB1) (59), histones (60), heat shock proteins (HSPs) (61) and oxidized phospholipids (62). Pattern recognition receptors (PRRs) identify these molecules, leading to the subsequent release of chemokines and pro-inflammatory factors that initiate and worsen the inflammatory response (63,64). PRRs are a class of innate immune receptors that detect endogenous molecules released following tissue injury and serve as sensors for DAMPs, including TLRs, C-type lectin receptors, retinoic acid-inducible gene I-like receptors, nucleotide-binding oligomerization domain-like receptors and DNA sensors (65,66). For example, HMGB1 is recognized by TLR2 and TLR4, while HSPs are recognized by TLR2. Stimulation of TLR2 or TLR4 triggers the activation of downstream MAPK and NF-κB pathways through the intermediary protein myeloid differentiation primary response 88 (Myd88), which subsequently enhances the activation of inflammatory cells and the secretion of inflammatory mediators (Fig. 3). Furthermore, oxidized lipids serve as important DAMPs involved in the inflammatory response by interacting with immune and ECs. For example, high concentrations of cyclopentenone prostaglandins can activate NLR family pyrin domain containing 3 inflammatory vesicles, which form a protein complex with the articulin ASC and pro-caspase-1, thereby mediating caspase-1-dependent IL-1β production, which in turn exacerbates the inflammatory response (58). Thus, inflammation can induce the onset of apoptosis and, conversely, apoptosis can further exacerbate the inflammatory response, with the two interacting, resulting in a vicious cycle (Table I).

Impaired clearance of apoptotic cells and persistence of inflammation. Under normal physiological conditions, apoptotic cells are cleared through phagocytosis, primarily by macrophages, thereby preventing the initiation of an inflammatory response. Effective clearance of apoptotic cells is key for managing inflammatory diseases, preventing secondary necrosis and restoring normal tissue function. Phagocytes are guided by chemokine 'find-me' signals in order to migrate towards apoptotic cells (67). The current four identified signals that facilitate locating cells are chemokine C-X3-C motif ligand 1 (CX3CL1; fractalkine), nucleotide triphosphates [including ATP and uridine triphosphate (UTP)], sphingosine-1 phosphate (S1P) and lysophosphatidylcholine (LysoPC). Among these, the release of ATP, UTP and CX3CL1 occurs during the early stages of apoptosis, while LysoPC and S1P are lipid chemokines produced in the later stages of apoptosis (67).

Phagocytes near apoptotic cells recognize specific ligands on their surface, referred to as 'eat-me' signals, including cell-surface calreticulin, ICAM-1 and complement component 1q, which activate signal transduction pathways and facilitate the phagocytosis of apoptotic cells (68). Following phagocytosis, apoptotic cells undergo cytosolic burial, maturing gradually and secreting anti-inflammatory and pro-tissue healing factors. However, when the clearing process is hindered, apoptosis can advance to necrotic apoptosis, which is marked by the rupture of the cell membrane and a marked release of intracellular DAMPs, thereby intensifying inflammation and causing tissue injury.

Table I. Key DAMPs and their clinical significance in ALI/ARDS.

First author, year	DAMP	Release mechanism	Recognition receptors	Clinical relevance (ALI/ARDS in sepsis)	(Refs.)
Deng *et al*, 2022	HMGB1	Nucleoprotein leakage from necrotic cells	TLR2/4	HMGB1 levels are notably elevated in serum and BALF from patients with sepsis, but their association with the extent of lung injury and prognosis remains controversial	(59)
Dutta *et al*, 2025	Histone	Neutrophil NETosis	NLRP3	Extracellular histones associate with ARDS severity and mortality and are expected to be early diagnostic markers of ARDS. In particular, histones H3 and H4 may serve as effective biomarkers and therapeutic targets in inflammatory diseases	(60)
Pei *et al*, 2022	HSP70	Stress cell cytoplasmic protein release	TLR2	Enhanced HSP70 expression attenuates sepsis-induced lung injury by inhibiting inflammation and apoptosis	(61)
Karki *et al*, 2023	Oxidized phospholipids	Apoptotic cell membrane lipid peroxidation	NLRP3	Oxidized phospholipids levels are elevated in patients with sepsis and ARDS, which can be used for early identification of high-risk patients and guide clinical decision-making	(62)

DAMP, damage-associated molecular patterns; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; HMGB1, high mobility group box 1; TLR, toll-like receptor; BALF, bronchoalveolar lavage fluid; NETosis, neutrophil extracellular traps formation; NLRP3, NOD-like receptor family pyrin domain containing 3; HSP70, heat shock protein 70.

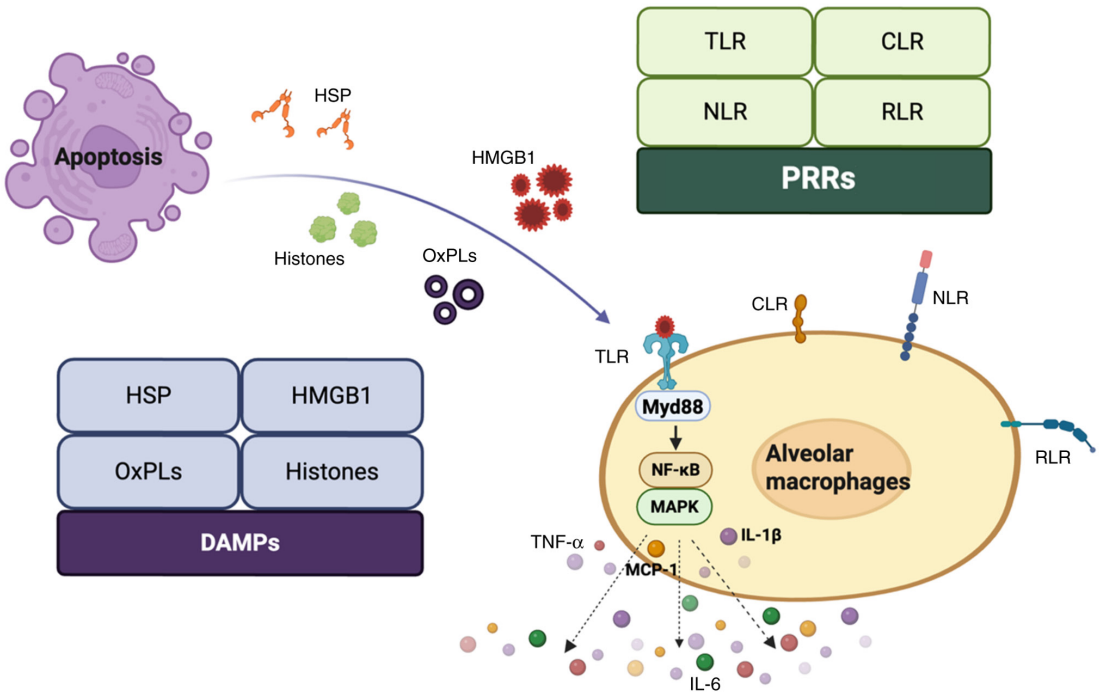

Figure 3. DAMPs released by apoptotic cells. Proteins or peptides released from apoptotic cells into the extracellular space can be transformed into DAMPs, including nuclear proteins such as HMGB1, histones, HSPs and oxidized phospholipids. These DAMPs can be recognized by PRRs, which subsequently activate downstream MAPK and NF-κB pathways through the adaptor protein Myd88, resulting in the secretion of inflammatory mediators. DAMPs, damage-associated molecular patterns; HMGB1, high mobility group box 1; HSPs, heat shock proteins; PRRs, pattern recognition receptors; MAPK, mitogen-activated protein kinase; Myd88, myeloid differentiation primary response 88; OxPLs, oxidized phospholipids; TLR, toll-like receptors; CLR, C-type lectin receptors; MCP-1, monocyte chemoattractant protein 1; RLR, RIG-I-like receptors; NLR, NOD-like receptors.

In normal lung tissue, the process of cytosolic burial helps to avert tissue injury and regulate the inflammatory response, largely facilitated by alveolar macrophages. Compared with other macrophage types, alveolar macrophages exhibit a longer lifespan and an enhanced self-renewal capacity. Under steady-state conditions, even during acute lung inflammation, the efficient cellular clearance of alveolar macrophages results in a minimal presence of apoptotic cells in the airways. When the function of alveolar macrophages is compromised and when apoptotic cells are generated in large quantities and cannot be rapidly cleared through cytosolic burial, a sustained release of DAMPs is prompted, perpetuating the inflammatory response (69). In certain patients with bacterial pneumonia, failure to resolve inflammation promptly or the occurrence of an inflammatory storm, results in impaired lung function and the subsequent development of ALI or ARDS, which further prolongs the inflammatory response in the lungs (70). A previous study has indicated that an increased quantity of uncleared apoptotic cells is found in the airways of patients with ARDS, respiratory failure or chronic lung inflammation, all of which are conditions frequently marked by impairments in the cellular clearance capabilities of alveolar macrophages (71). Therefore, the timely and effective clearance of apoptotic cells is key in modulating the inflammatory response and protecting lung function.

5. Effects of inflammation and apoptosis: Pathophysiological functions of lung tissue

Alveolar epithelial cell damage and dysfunction

Alveolar epithelial barrier disruption. Alveolar epithelial cell damage is a key determinant of the severity of ALI and ARDS. Therefore, protecting the function and barrier integrity of AECs is of great importance (72). AECs, the structural components of the lung, comprise alveolar type I and II epithelial cells. Type I epithelial cells, which serve as the main location for gas exchange, experience higher vulnerability to inflammation, oxidative stress and various injuries (mechanical injury, chemical injury, hyperoxic injury, etc.), resulting in an increased likelihood of cell death. Conversely, type II epithelial cells exhibit greater resilience, possessing the ability to proliferate and convert into type I epithelial cells, thus serving a role in the repair and preservation of alveolar epithelial barrier integrity (73). Furthermore, AECs regulate ion transport through the Na^+/K^+-ATPase on the cell surface, establishing an osmotic gradient between the intracellular and extracellular environments. This regulates the alveolar fluid clearance process, preventing the accumulation of alveolar edema fluid (74).

The integrity of the AEC barrier is also supported by the glycocalyx, a layer of glycosaminoglycans and proteoglycans covering the alveolar surface and the basement membrane shared with ECs (75). However, during sepsis, the organism releases a large quantity of pro-inflammatory factors and chemokines, leading to an exaggerated and dysregulated inflammatory response. Mitochondria, essential organelles in AECs, not only generate ATP but also function in intracellular and extracellular signaling under stress (76). Evidence indicates that sustained mitochondrial dysfunction serves an important role in the process of necrotic apoptosis within AECs (77,78). Inflammatory stimuli activate the mitochondria-associated apoptotic pathway, which further releases apoptotic factors and upregulates pro-inflammatory factor levels. This excessive cytokine production can directly or indirectly induce epithelial cell apoptosis by recruiting leukocytes to migrate to the lungs and disrupting TJ proteins (such as connexin, sealin and E-calmodulin) between AECs. Consequently, this results in damage to epithelial structures, detachment of the glycocalyx, impairment of the alveolar epithelial barrier integrity, increased permeability, decreased production of surface-active substances and reduced ion and fluid transport capacity from the alveolar lumen. These changes lead to dysfunction in gas exchange, ultimately causing alveolar edema, alveolar collapse and refractory hypoxemia. Lei *et al* (79) demonstrated that the treatment of SALI mice with 3-methyladenine (3-MA), a drug that regulates apoptosis, significantly enhanced the integrity of the alveolar epithelial barrier. This study found that it effectively inhibited lung inflammation and epithelial cell apoptosis in mice, improved pulmonary pathological changes and alleviated lung injury. Conversely, activated epithelial cells contribute to increased secretion of chemokines and adhesion molecules, leading to cell death and inflammatory responses, therefore resulting in a vicious cycle.

Therefore, the repair of the alveolar epithelial barrier is a critical indicator for the prognosis of lung injury. A previous clinical study has shown that therapeutic strategies targeting epithelial repair, such as mesenchymal stem cell (MSC)-secreted keratinocyte growth factor, can improve the oxygenation index in patients with ARDS (80).

Abnormal synthesis and secretion of alveolar surface-active substances. Alveolar type II epithelial cells are capable of secreting the alveolar surface-active substance pulmonary surfactant (PS). The functions of PS include reducing alveolar surface tension, maintaining the relative stability of the alveolar structure, facilitating the absorption of alveolar fluid, maintaining fluid balance in the lungs, preventing pulmonary edema and atelectasis and enhancing the lung's defense function (81,82). PS is a complex formulation that consists primarily of 90% phospholipids and 10% proteins (83). It contains four surfactant proteins (SPs) that are linked to surface-active agents, namely SP-A, SP-B, SP-C and SP-D. Among these, SP-A and SP-D are hydrophilic proteins that are part of the collectin family and are key in innate immune defense. Conversely, SP-B and SP-C are highly hydrophobic apolipoproteins that are key in the biophysical functionalities of surfactants (84). A previous study found that SP-A knockout mice exhibited a higher severity of lung injury and mortality in a severe acute respiratory syndrome coronavirus (COVID) 2-induced mouse ALI model, indicating that SP-A serves a key role in pathogen defense (85).

Under physiological conditions, 80-90% of PS is distributed in large aggregates (LAs) with high surface activity. However, during infection, the upregulation of inflammatory mediators and activation of apoptosis-inducing signals leads to the disruption or inhibition of PS. The content of PS in LAs is markedly reduced, shifting to small aggregates with markedly low surface activity, which are mainly products of PS degradation. Furthermore, activated immune cells generate ROS, which may disrupt surfactant functionality by diminishing the synthesis of SP and phospholipids (86). Additionally,

high levels of NO free radicals and TNF-α produced during inflammation can directly impede the production of SP-A, SP-B and SP-C (87). As a result, the synthesis and activity of alveolar surface-active substances are reduced, leading to an increase in alveolar surface tension. On the other hand, the increased alveolar surface tension fails to maintain the normal alveolar structure, leading to alveolar collapse. During mechanical ventilation, atelectatic alveoli may be damaged by the force generated by the cyclic opening and closing of the ventilator, ultimately exacerbating respiratory failure. Dargaville *et al* (88), through a 2-year follow-up study of preterm infants with ARDS treated with minimally invasive surfactant application, found that infants treated with surfactant had a lower incidence of adverse respiratory outcomes within a period of 2 years. This finding, to some extent, suggests that alveolar surfactant can improve lung injury and maintain normal alveolar function.

Pulmonary vascular EC damage and vascular dysfunction

Vascular endothelial barrier disruption and increased permeability. The endothelium acts as a physical barrier that separates blood, gases and stromal tissues, serving a vital role in preventing inflammation and coagulation, aiding in gas exchange, controlling vascular tone and engaging in endocrine signaling (89). In particular, the pulmonary endothelium functions as a semi-permeable barrier key for gas exchange at the alveolar-capillary interface and in managing the flow of fluids and solutes between the blood and the interstitial compartments of the lungs. The connections among lung ECs include adherens junctions (AJs), TJs and gap junctions. Among these, AJs are mainly composed of VE-cadherin, which bind to intracellular connexins (such as p120-connexin), waveform proteins and other proteins in the actin cytoskeleton to maintain the integrity of the pulmonary endothelial barrier. During an inflammatory response, various factors such as the activation of pro-inflammatory factors (including TNF-α and IL-1β) and increased ROS production can lead to the phosphorylation of VE-cadherin and its associated proteins. This results in the detachment of VE-cadherin from the actin cytoskeleton and the breakdown of AJ proteins. At the same time, the contraction of actin stress fibers creates a pulling force on VE-cadherin, compelling it to dissociate from the proteins it is bound to. This results in impaired inter-endothelial connections, increased permeability and damage to the endothelial barrier. Therefore, VE-cadherin has become an important biomarker for endothelial barrier disruption and is key for maintaining the integrity of the endothelial barrier. Previous research has suggested that the concentration of serum VE-cadherin in patients with ARDS is notably elevated compared with healthy controls. With this, its levels are negatively associated with the pulmonary vascular permeability and oxygenation indexes (90).

In addition, TJ proteins (such as claudin and occludin) interact with zonula occludens (ZO-1) in the cytoplasm. ZO-1 binds to α-catenin and the actin cytoskeleton to stabilize endothelial barrier function (91). When inflammatory mediators such as histamine are present, TJ proteins experience phosphorylation dependent on Src and undergo depletion, resulting in a compromised endothelial barrier function and increased endothelial permeability (92). Previous research indicates that the expression levels of TJ proteins are markedly reduced in the lung endothelium of patients with ARDS (93). Meanwhile, damaged or dead ECs further release toxic cellular components, allowing more leukocytes to migrate from the circulation to the site of inflammation, thus exacerbating the inflammatory response. Additionally, inflammatory mediators may further activate the apoptotic pathway, leading to EC damage and death.

Vasodilatory dysfunction and microthrombosis. A healthy pulmonary endothelium largely suppresses inflammation, maintains blood flow and prevents thrombosis. Some studies have shown that various stimuli, including hypoxia, cytokines, chemokines, thrombin, LPS, DAMPs and apoptosis, can lead to the activation and damage of ECs (94,95). On the one hand, ECs produce endothelium-derived diastolic factors (EDRFs) such as NO and prostacyclin as well as endothelium-derived contractile factors such as endothelin, epoxyeicosatrienoic acid and thromboxane A_2 to regulate vascular tone (96). Activated ECs exhibit impaired synthesis or release of EDRFs, resulting in sustained vasoconstriction, reduced vessel diameter, slowed blood flow and impaired pulmonary microcirculation. On the other hand, activated ECs recruit activated neutrophils and form neutrophil extracellular traps with activated platelets, shifting to a pro-coagulant phenotype. Anticoagulant molecules such as thrombomodulin (TM) are other important markers of endothelial injury. Under normal conditions, TM is expressed on the surface of ECs, where it exerts anticoagulant effects by activating the protein C system through binding to thrombin (97). During endothelial injury, TM is shed from the cell surface into circulation, forming soluble TM (sTM), exposing collagen fibers and other subendothelial matrix proteins. The expression of platelet adhesion molecules is upregulated and platelets are activated and rapidly adhere to form a microthrombus, initiating the hemostatic process. Previous research has shown that patients with ARDS who exhibit high levels of sTM have a 3.5-fold increased risk of 60-day mortality, which can serve as a biomarker for early prognostic assessment, and perhaps provide a reference for clinical risk stratification and treatment decision-making (98).

Coagulation factors interact with tissue factor (TF), which is present on AECs and macrophages, initiating an exogenous coagulation cascade. Within the intact vessel wall, TF remains hidden. Following damage to the vascular endothelium, TF becomes accessible to blood and can bind directly to coagulation factor VII to create the TF-VIIa complex, which is capable of activating clotting factors IX and X in the bloodstream, resulting in the formation of active enzymes (coagulation factors IXa and Xa) that subsequently convert plasminogen to thrombin. Thrombin then cleaves fibrinogen into fibrin, which polymerizes to create a fibrin network that forms a thrombus, incorporating aggregated platelets (99). Naderpour *et al* (100) studied patients with COVID-19 during the pandemic and found that the combined use of tissue plasminogen activator and heparin in patients with severe respiratory failure improved oxygenation and reduced overall mortality. Thus, impaired pulmonary microcirculation further exacerbates tissue ischemia and hypoxia, promoting EC injury, pro-inflammatory factor release and activation of apoptotic pathways, thereby exacerbating lung tissue injury.

Table II. Inhibitors of inflammatory and apoptotic signaling pathways.

Drug class	Representative drugs	Mechanism of action	Effect	(Refs.)
NF-κB inhibitor	Aspirin	Blocks IκBα phosphorylation and degradation, inhibits NF-κB activation	Reduces pulmonary edema, inhibits inflammatory factor release	(101)
	FGF18	Inhibits NF-κB p65 phosphorylation and nuclear translocation	Reduces inflammatory response, promotes lung repair	(103)
MAPK inhibitor	SB203580 (p38 inhibitor)	Inhibits p38 MAPK phosphorylation	Reduces TNF-α, IL-1β level, inhibits caspase-3 activation	(105)
	SP600125 (JNK inhibitor)	Blocks JNK signaling	Inhibits Bax/Bak activation, reduces mitochondrial apoptosis	(106)
Apoptosis pathway inhibitor	Soluble Fas	Fas/FasL inhibitor	Blocks exogenous apoptotic pathway, attenuates alveolar epithelial cell injury	(107)
	Z-VAD-FMK	Broad-spectrum caspase inhibitor	Blocks apoptosis execution stage, attenuates lung tissue damage	(108)
Herbal active ingredient	Quercetin	Inhibits NF-κB-related pathway	Attenuates SALI	(104)

FGF18, fibroblast growth factor 18; MAPK, mitogen-activated protein kinase; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1 beta; Bak, Bcl-2 antagonist/killer; Fas/FasL, Fas receptor/Fas Ligand; Z-VAD-FMK, Z-Val-Ala-Asp-fluoromethylketone; SALI, sepsis-induced acute lung injury.

6. Advances in therapeutic strategies targeting the synergistic effects of inflammation and apoptosis

Drug intervention targets and strategies

Inhibitors of inflammatory and apoptotic signaling pathways. The activation of essential signaling pathways, such as NF-κB and MAPK, is closely linked to ALI associated with sepsis, which subsequently triggers the apoptotic pathway and exacerbates lung damage. NF-κB, a major regulator of inflammation, serves a pivotal role in the onset and progression of numerous inflammatory diseases. Inhibitors of NF-κB reduce the production of inflammatory factors while also suppressing the expression of apoptosis-related genes, thus presenting a potential therapeutic avenue for lung injury driven by synergistic inflammation and apoptosis (Table II). For example, non-steroidal anti-inflammatory medications (such as aspirin) specifically prevent the phosphorylation and breakdown of IκBα, which in turn reduces the activity of NF-κB. In the lung tissue of mice treated with aspirin, NF-κB activation was notably inhibited, leading to improved pulmonary edema (101). Glucocorticoid receptor agonists, such as dexamethasone, can inhibit NF-κB through direct interaction with its RELA enhancer-binding protein like arrestin subunit, effectively blocking its functional activity. Furthermore, fibroblast growth factor (FGF) 18, which belongs to the FGF family, has demonstrated the ability to reduce cellular inflammation (102). Previous research has shown that FGF18 suppresses the phosphorylation of NF-κB p65 and reduces its translocation to the nucleus in both *in vivo* and *in vitro* settings. This activity consequently inhibits the activation of the NF-κB pathway, reduces lung injury and supports lung repair (103). In TCM, it is considered that numerous herbs are related to this mechanism, among which quercetin is a well-researched example (104).

The MAPK pathway (including p38, JNK and ERK) also serves a key role in inflammatory responses and apoptosis. Previous research indicates that p38 inhibitors such as SB203580 can mitigate LPS-induced lung injury through various mechanisms, including inhibition of TNF-α and IL-1β release and reduction of caspase-3 activity (105). SP600125 is an orally active, reversible ATP-competitive JNK inhibitor that can influence the expression of key proteins in the mitochondrial apoptotic pathway, upregulate the expression of the anti-apoptotic protein Bcl-2 and downregulate expression of the pro-apoptotic protein Bax, thereby reducing apoptosis (106).

In addition, specific inhibitors of apoptotic pathways may also become therapeutic targets for SALI. Fas receptor/Fas ligand inhibitors (such as soluble Fas), as inhibitors of the death receptor pathway, can block the extrinsic apoptotic pathway and reduce alveolar epithelial cell damage (107). As a factor in apoptosis, the broad-spectrum caspase inhibitor Z-Val-Ala-Asp-fluoromethylketone can block the execution phase of apoptosis and alleviate lung tissue damage (108).

Antioxidants and free radical scavengers. Free radicals serve a key role in intracellular signal transduction and various physiological processes at optimal concentrations. However, excess of these free radicals can lead to oxidative damage to proteins. The body's antioxidant defense system comprises both endogenous antioxidants and exogenous free radical scavenging mechanisms. Endogenous antioxidants primarily eliminate excess free radicals and are categorized into enzymatic and non-enzymatic ROS scavengers. Enzymatic antioxidants, including superoxide dismutase (SOD) (109), catalase (CAT) (110) and glutathione peroxidase (GPX) (111), facilitate the conversion of O_2 radicals into H_2O_2 and O_2, which are further catalyzed into H_2O and O_2. Non-enzymatic ROS scavengers include coenzyme Q10 (also known as ubiquinone) (112,113) and acetylated phospholipids (plasmalogens) (114), among others. Coenzyme Q10 is integral to the mitochondrial electron transport chain, functioning as a component of the mitochondrial respiratory chain while scavenging lipid peroxidation free radicals (113,115). Exogenous free radical scavengers, primarily sourced from dietary intake, encompass hydrophilic agents, such as vitamin C (116) and glutathione, as well as lipophilic agents, including vitamin E (117), flavonoids (118,119) and carotenoids (120), which effectively scavenge O_2^- and HO^-.

Mitochondria, as the primary site of ROS production, are often subjected to high levels of ROS, leading to oxidative damage of mitochondrial DNA. This damage subsequently activates the mitochondrial-associated apoptotic pathway, thus exacerbating lung injury. Antioxidants serve a key role in mitigating inflammation-induced oxidative stress by scavenging free radicals and maintaining the body's redox balance. This action effectively inhibits the mitochondrial apoptotic pathway, thereby protecting lung tissue from the combined detrimental effects of inflammation and apoptosis. Numerous antioxidant drugs have been employed in clinical treatments, including recombinant SOD, vitamin C, vitamin E, α-lipoic acid (121), bioflavonoids, selenium (122), glutathione, coenzyme Q10 (123) and various TCM herbal medicines such as *Curcuma longa* (124), *Astragalus* (125) and *Rhodiola rosea* (126). Curcumin (124), through its β-diketone group and *Astragalus* (125), through active components such as polysaccharides, saponins and flavonoids, directly scavenge ROS while simultaneously activating the endogenous antioxidant enzyme system, which includes SOD, CAT and GPX. This dual action results in a multi-level, multi-target antioxidant protective effect. Similarly, study has demonstrated that *Rhodiola* injection not only exhibits direct ROS scavenging capabilities, but also protects mitochondrial function, regulates the AMP-activated protein kinase/mTOR autophagy signaling pathway and maintains the balance between cell apoptosis and survival (126). This creates a comprehensive protective network ranging from oxidative stress prevention to cellular damage repair.

However, there is currently very few related clinical trial available (127). These therapeutic agents face important challenges in clinical application. Previous research has indicated that vitamin E supplementation does not reduce all-cause mortality in patients and high doses of vitamin E may even increase overall mortality (128). A similar issue is observed with vitamin C, whereby excessively high levels in the body can induce oxidative stress-related DNA damage, similar to the effects of lower levels. Potential limitations of antioxidant therapy may arise from the need to preserve an equilibrium between oxidation and reduction. Elevated levels of ROS can activate endogenous antioxidant defenses to protect damaged tissues. Notably, scavenging ROS may increase the risk of infection and disrupt ROS-dependent signaling pathways. Consequently, the timing, concentration and dosage of antioxidants, along with their bioavailability and effective targeted delivery to specific organs, are important factors that are often challenging to regulate in clinical practice.

Cell therapy and biological agents

MSC therapy. There is increasing evidence to suggest that therapy involving MSCs shows considerable potential for treating SALI and ARDS and it is currently being evaluated in clinical trials (129,130). MSCs have multiple functions and originate from various sources including adipose tissue, bone marrow, umbilical cord blood and placental tissue. These cells are able to differentiate into a wide variety of cell types belonging to the mesenchymal lineage (131,132). As a novel therapeutic agent for ALI, MSCs may exhibit immunomodulatory, angiogenic and regenerative effects (133-135). Mechanistically, MSCs can differentiate into lung cells, directly replacing damaged cells and tissues, thereby facilitating repair at the injury site. Additionally, MSCs can migrate to damaged lung areas and reduce the permeability of lung ECs and epithelial cells by secreting various paracrine factors that promote neoangiogenesis and tissue repair, a phenomenon validated in multiple preclinical ALI models (136-138).

Furthermore, MSCs possess complex immunomodulatory functions. In a pro-inflammatory setting, MSCs have the ability to release anti-inflammatory cytokines, including IL-10, TGF-β1 and PGE2 (118), release exosomes with microRNAs with anti-inflammatory effects (136), inhibit the activation of NF-κB, reduce the release of pro-inflammatory factors (139) and upregulate the expression of anti-apoptotic molecules, thereby exerting direct anti-inflammatory and anti-apoptotic effects. Concurrently, MSCs also reduce mitochondrial division, mitigate oxidative stress damage in macrophages and induce macrophage polarization towards anti-inflammatory phenotypes, indirectly contributing to anti-inflammatory and antioxidant effects (140,141) (Fig. 4).

The effects of MSCs on reducing inflammation, modulating the immune response and promoting tissue repair have been validated, showing considerable effectiveness in preclinical studies involving animals. However, the marked individual variability and prevalence of non-responsive patients observed in clinical trials pose substantial challenges for the broader application of MSC therapy in clinical practice (142). An initial clinical study suggests that MSC therapy is generally safe and does not remain in the body for a prolonged period of time (143). However, a certain experimental study has reported the detection of MSCs ≤120 days post-administration (144). This persistence raises concerns regarding potential tumorigenesis, an area where conclusive findings and solutions remain elusive. Consequently, further accumulation of safety data regarding long-term treatment and the large-scale application of MSC therapy is important.

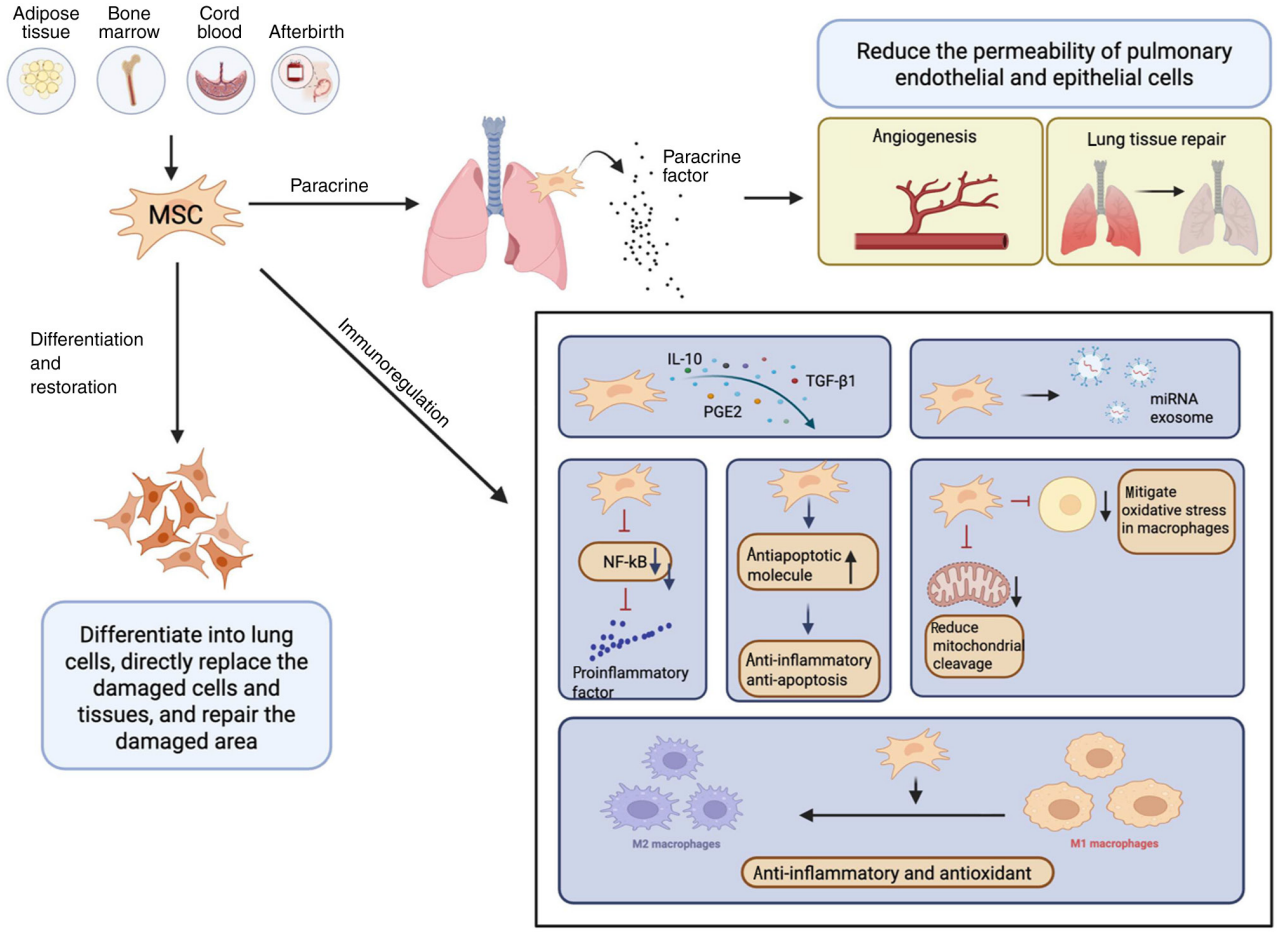

Figure 4. MSC therapy. MSCs are derived from various sources, including adipose tissue, bone marrow, umbilical cord blood and placental tissue. On the one hand, MSCs can differentiate into lung cells, directly replacing damaged cells and tissues, thereby promoting the repair of injured sites. Additionally, MSCs can migrate to the damaged lung area, where they reduce the permeability of pulmonary endothelial and epithelial cells by secreting various paracrine factors that promote angiogenesis and tissue repair. On the other hand, MSCs release anti-inflammatory cytokines and miRNA exosomes, which inhibit NF-κB activation, decrease the release of pro-inflammatory factors and upregulate the expression of anti-apoptotic molecules. Simultaneously, MSCs also reduce mitochondrial fission, alleviate oxidative stress damage in macrophages and induce the polarization of macrophages toward an anti-inflammatory phenotype. MSCs, mesenchymal stem cells; miRNA, micro-RNA; PGE2, prostaglandin E2.

Additionally, the optimal therapeutic regimen for MSCs in treating SALI, including therapeutic dosage, timing of treatment and route of administration, remains to be established. Despite the encouraging effectiveness shown by MSCs in preliminary animal research, it is important to recognize that mouse models frequently do not accurately mimic human diseases. The quantity of MSCs utilized in these mouse experiments vary greatly from those administered to clinical patients, along with there being considerable individual differences among humans, which could additionally affect treatment results (144). Therefore, the clinical therapeutic effects of MSCs are yet to be fully elucidated, necessitating additional follow-up data to accurately assess their efficacy.

Anti-apoptotic gene therapy and biologics. Oxidative stress is a key mechanism in SALI. Traditional antioxidants, such as vitamin C or vitamin E, have limited clinical efficacy due to their lack of targeting specificity and dose-dependent effects. To overcome this bottleneck, progress has been made in recent years with novel targeted antioxidants and biologics. For instance, developments have been made in mitochondrial-targeted antioxidants such as MitoQ, which has been shown to protect cells from apoptosis and inhibit H_2O_2-induced growth factor receptor signaling. This is primarily achieved through its unique triphenylphosphonium carrier system, which precisely delivers the compound to the interior of mitochondria, directly scavenging mtROS and effectively blocking the mtROS-Ca^{2+}/calmodulin-dependent kinase II-mediated apoptotic signaling pathway. In an investigation using MitoQ to intervene in LPS-induced ALI in mice, it was found that, compared with the model group, MitoQ treatment significantly reduced the levels of oxidative markers in mouse serum (a 50% decrease in MDA content; $P<0.05$), while also improving lung injury in mice (145).

Edaravone, approved in Japan as a free radical scavenger for ischemia-reperfusion injury, primarily works by inhibiting lipid peroxidation and preventing the abnormal opening of the mitochondrial MPTP, thereby reducing apoptosis in alveolar epithelial cells. In a randomized clinical trial, edaravone was used to treat critically ill patients with COVID-19 admitted to the ICU. Results showed that the edaravone treatment group experienced a reduction in mechanical ventilation dependency and a shortened ICU treatment duration (146).

Numerous studies have shown that specific biological substances can alleviate pulmonary injury by mitigating inflammatory oxidative stress, offering new avenues for the clinical management of SALI. For example, the nebulized formulation of recombinant human SOD can specifically neutralize O_2^- within lung tissue, directly targeting the sites of inflammation. Furthermore, FGF21, which was initially identified and cloned in 2000, performs various biological roles, including promoting tissue repair and regulating metabolism (147). Research conducted by Gao *et al* (148) suggested that the administration of exogenous FGF21 leads to a reduction in lung inflammation and apoptosis by influencing the TLR4/MyD88/NF-κB signaling pathway, thereby mitigating SALI. As a result, the relevance of FGF21 in severe conditions such as ALI and ARDS has gained interest (149).

7. Conclusion

The present study systematically summarized the synergistic mechanisms of inflammation and apoptosis in SALI, emphasizing the pivotal role of signaling pathways such as NF-κB/MAPK and the cascade of inflammatory factors (TNF-α, IL-1β and MCP-1) they mediate, which drive oxidative stress and apoptosis activation, ultimately leading to the disruption of alveolar epithelial and pulmonary vascular endothelial barriers. Despite progress in therapeutic strategies targeting synergistic effects (such as MSC therapy and targeted antioxidants), key research gaps and translational challenges remain. For example, the detailed molecular regulatory networks between inflammation and apoptosis, as well as the impact of individual differences on their synergistic effects, have not yet been fully elucidated. Furthermore, there is a lack of targeted specificity regulation tools, such as precise identification of biomarkers for different pathological stages of SALI and insufficient targeting of lung-specific drug delivery systems to acute inflammatory lesion areas.

Future research should focus on elucidating the molecular complexity of the synergistic effects between inflammation and apoptosis to develop more targeted and effective therapeutic strategies. Additionally, multicenter, large-sample clinical studies should be conducted to explore the clinical translation potential of apoptosis/inflammation pathway inhibitors. Integrating multidisciplinary resources from immunology, bioengineering, data science and other fields will advance the synergistic development of regulatory science and technological innovation. There is an expectation that such initiatives will generate innovative concepts and approaches to enhance the prognosis of patients with SALI.

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Authors' contributions

LZ contributed to conceptualization, visualization, writing the original draft, reviewing and editing. HL contributed to investigation, writing, reviewing and editing the manuscript. DL contributed to formal analysis, the software used, writing, reviewing and editing the manuscript. QD contributed to funding acquisition, project administration, resources, supervision, writing, reviewing and editing the manuscript. 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.

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