Journal of Inflammation Research Dovepress

Open Access Full Text Article REVIEW

Regulated Cell Death of Alveolar Macrophages in Acute Lung Inflammation: Current Knowledge and Perspectives

Siwei Xia, Xiaoyan Gu, Gaojian Wang, Yizhi Zhong, Fengjie Ma, Qinxue Liu, Junran Xie

Department of Anesthesiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China

Correspondence: Junran Xie, Department of Anesthesiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China, Email xiejunran@zju.edu.cn

Abstract: Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a common and serious clinical lung disease characterized by extensive alveolar damage and inflammation leading to impaired gas exchange. Alveolar macrophages (AMs) maintain homeostatic properties and immune defenses in lung tissues. Several studies have reported that AMs are involved in and regulate ALI/ARDS onset and progression via different regulated cell death (RCD) programs, such as pyroptosis, apoptosis, autophagic cell death, and necroptosis. Notably, the effects of RCD in AMs in disease are complex and variable depending on the environment and stimuli. In this review, we provide a comprehensive perspective on how regulated AMs death impacts on ALI/ARDS and assess its potential in new therapeutic development. Additionally, we describe the crosstalk between different RCD types in ALI, and provide new perspectives for the treatment of ALI/ARDS and other severe lung diseases.

Keywords: alveolar macrophage, apoptosis, autophagic cell death, necroptosis, pyroptosis, acute lung injury

Introduction

Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) are serious diseases caused by excessive and uncontrolled systemic inflammatory responses triggered by direct or indirect lung injury.[1] Clinical manifestations include decreased lung compliance, severe hypoxemia, and dyspnea.[2] Critically, these syndromes are associated with high morbidity and mortality rates and place severe strains on healthcare systems. Currently, ALI/ARDS treatments are mainly supportive; they improve oxygenation, reduce lung injury, and treat the primary disease.[3] Therefore, effective interventions are required to improve prognosis outcomes for affected patients.

Regulated cell death (RCD) is required for homeostatic maintenance in organisms.[4] Cell death plays a central role in tissue development, aging, tissue damage and cancer prevention, and tissue homeostasis. However, hyperactive RCD can induce a systemic inflammatory state with pathological consequences.[5] A considerable number of experiments have revealed that various cell types in the lungs undergo regulated cell death, which affects the progression of ALI/ARDS, including alveolar type 2 epithelial cells, neutrophils, and T cells involved in adaptive immunity, as well as alveolar macrophages.[6–9] As one of the most active cell types in the immune response, alveolar macrophages not only play a crucial role in defending aga/inst infections and clearing damaged cells but also participate in the repair process of tissue damage as part of the body's immune regulatory pathways.[10] Previous studies have reported that in ALI/ARDS, alveolar macrophages (AMs) may undergo multiple RCD programs, including apoptosis, autophagic cell death, pyroptosis, and necroptosis.[8,11]

A growing body of research now suggests mutually reinforcing relationships between RCD and inflammation, which together drive a regionally self-reinforcing feedback loop that exacerbates ALI severity.[12] AMs have key roles in ALI pathogenesis, and their regulatory death is a key strategy to address inflammation.[13] Currently, we lack effective

Received: 25 September 2024
Accepted: 29 November 2024
Published: 21 December 2024

pharmacological treatments to improve the survival of patients with ALI/ARDS, thus targeting multiple RCD pathways in AMs may help in the treatment of several currently incurable lung diseases, such as pulmonary fibrosis and COPD.

The aim of this review is to summarize the core mechanisms whereby different types of AMs death, and their crosstalk, have influenced ALI development, and to highlight the potential therapeutic value of targeting RCD pathways involved in these processes.

AMs Characteristics and Functions

AMs are resident macrophages in the airways and lungs with very low turnover rates and long lifespans.[14] AMs have key roles in defenses against airborne particles and microorganisms, in apoptotic cell clearance, wound healing regulation, and eliciting immune responses to lung pathogens.[15] As the primary immune sentinels of the respiratory tract, AMs have unique phenotypic and transcriptional profiles; they express specific surface markers (eg, Siglec-F and CD11) and are involved in surfactant clearance.[16,17] AMs have excellent plasticity and are susceptible to epigenetic and immunometabolic microenvironment factors, and also exhibit significant functional differences.[18,19]

AMs have key roles regulating lung inflammation and maintaining immune homeostasis, and remain relatively stationary under healthy airway epithelial cell maintenance.[20] AMs, through pathogen-recognizing receptors on their surfaces, become rapidly activated after inflammatory episodes, releasing a wide range of cytokines and chemokines to abate inflammation and promote tissue repair.[21] AMs also have important roles clearing dead alveolar cells and excess alveolar surfactants.[22] Early apoptotic neutrophil recognition and phagocytosis by AMs can effectively prevent the uncontrolled release of toxic substances from dead neutrophils, thereby affecting lung injury outcomes.[23,24] Recent studies have found a relationship between an impairment in AMs efferocytosis and the polarization of AMs in patients with ARDS. IL-8 induces classical activation of macrophages, thus blocking IL-8 may promote the clearance of apoptotic cells and reduce inflammation.[25] Additionally, AMs inhibit excessive inflammation by regulating other immune cells,[26] while AMs depletion elicits stronger inflammatory responses in animals.[27]

RCD has vital roles regulating macrophage functions at multiple levels of macrophage generation, recruitment, and differentiation levels, thereby affecting the course of many diseases. For example, autophagy affects macrophage polarization, phagocytosis, and antigen presentation.[28] RCD in AMs is closely related to lung innate immune functions, and RCD dysfunction or imbalance has been associated with a pathological state in several lung diseases (Figure 1). Lipopolysaccharide (LPS) promotes apoptosis and inflammation in AMs, which aggravates lung fibrosis in mice.[29] Apoptosis levels in AMs are also significantly elevated in ALI models.[30] Additionally, in inflammasome-dependent AMs, pyroptosis has key roles in endotoxin or mechanical ventilation-induced ALI.[31] Many studies have shown that AMs-mediated RCD is induced in different ALI models, thus targeting these RCD pathways may be effective for ALI/ARDS treatment.

AMs Apoptosis in ALI

The Apoptosis Pathway

Apoptosis is the most widely recognized and major RCD type in mammals.[32] Apoptosis is further classified into extrinsic and intrinsic types. Several studies have reported crosstalk between intrinsic and extrinsic apoptosis[33] (Figure 2). Bcl-2 homology 3 interacting domain death agonist (BID), a BH3-only Bcl-2 family member, provides a basis for crosstalk between extrinsic and intrinsic pathways. When a death ligand binds to the death receptor, caspase-8 cleaves BID to form tBID, which activates Bax and Bak on outer mitochondrial membranes.[34] Additionally, FLIP, a major apoptosis-regulating protein, not only binds Fas-associated death domain (FADD) in the extrinsic apoptosis pathway to regulate cell death, but also affects the intrinsic apoptosis pathway by regulating BID activation.[35] Gajate et al reported that during Fas/CD95-mediated apoptosis, the Fas/CD95 death receptor recruited FADD, formed Death-inducing signaling complex (DISC), and aggregated into lipid rafts. BID and apoptosome components are also translocated to lipid rafts,[36] where rafts act as support structures to intersect death receptor and mitochondrial apoptosis signaling pathways.

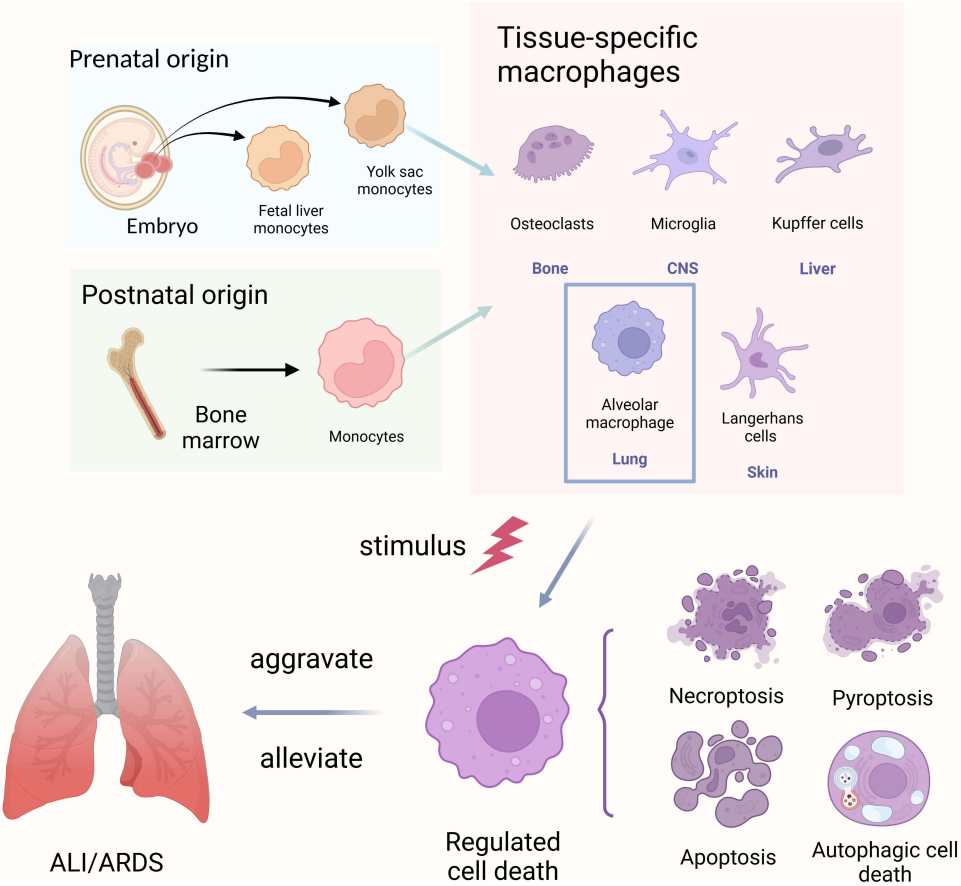

Figure 1 Alveolar macrophages. Macrophages resident in different organs can be derived from embryonic monocyte progenitors that originate in the yolk sac or fetal liver during embryonic development and then migrate to different tissues. Circulating monocytes that develop from haematopoietic stem cells in the bone marrow can also differentiate into tissue-resident macrophages. They exhibit diverse functions. When resident alveolar macrophages are exposed to external stimuli (such as environmental factors, drugs, genetic factors, etc), they undergo regulated cell death, which affects their phenotype and function, thereby either exacerbating or alleviating pulmonary inflammation. Created in BioRender. Xia, S. (2024) https://BioRender.com/e15t922.

Apoptosis in AMs

In ALI, Apoptosis Levels are Increased in AMs

In LPS-induced in vivo and in vitro ALI models, apoptosis-related proteins Bax and caspase-3 are significantly up-regulated, whereas anti-apoptosis-related Bcl-2 is significantly down-regulated, suggesting that apoptosis is significantly activated in AMs.[30] Previous studies reported that circular RNAs are differentially expressed in lung macrophages in mice and involved in ALI regulation.[37] Wei et al observed that up-regulated circ-Phkb expression inhibited AMs proliferation via TLR4/MyD88/NF-κB/CCL2 signaling, thereby promoting apoptosis and pro-inflammatory factor release.[30] Thus, Circ-Phkb promotes lung inflammation and may be a potential target for ALI therapy. Another intriguing study found that the activation of the Wnt/β-catenin pathway may be one of the key mechanisms underlying LPS-induced apoptosis in AM cells. Bone marrow mesenchymal stem cells (BMSCs) can effectively inhibit LPS-triggered phosphorylation of GSK-3β and prevent the expression of β-catenin in AMs.[38] Therefore, the transplantation therapy with BMSCs holds promise as an effective strategy for treating ALI/ARDS.

Another study reported that Resveratrol, a potent SIRT-1 (silent mating-type information regulation 2 homolog-1) activator, significantly alleviates sepsis-induced ALI by decreasing apoptosis and autophagy levels in AMs via VEGF-B signaling and inhibiting LPS-dependent C5aR gene expression.[39] Interestingly, this study suggested that the inhibitory effects on LPS-induced apoptosis in AMs were possibly, and partly, via inhibited LPS-induced autophagy.

AMs Apoptosis Impairs Body Immune Competence

Interestingly, apoptosis in AMs reduces their ability to phagocytose inflammatory effector cells, that may weaken the self-repairing capacity in lung tissue. Lu et al reported a significant reduction in AMs and a time-dependent increase in

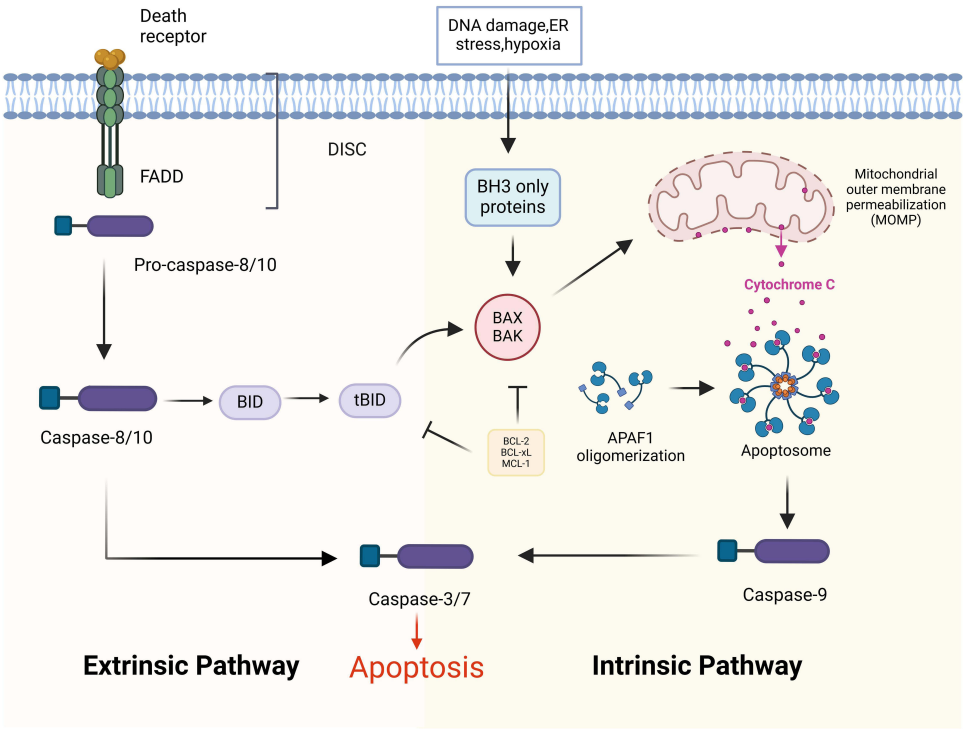

Figure 2 The extrinsic and intrinsic apoptotic pathways. The extrinsic apoptotic pathway is activated when the ligand activates the death receptor, recruiting FADD and Caspase-8/10 to form the death-inducing signalling complex (DISC). Subsequent activation of Caspase-8/10 and death effector Caspase-3/7 induces apoptosis. The intrinsic apoptotic pathway involves the activity of the BCL-2 family of proteins located in the outer mitochondrial membrane, and many stimuli lead to permeability of the mitochondrial outer membrane (MOMP) and further release of cytochrome C. The latter binds to APAF-1 to form the DISC. The latter binds APAF-1 to form apoptotic bodies, which then activate Caspase-9 and downstream Caspase-3/7. In some cells, Bid cleavage also activates BAK/BAX thereby leading to the release of cytochrome c from mitochondria and promoting apoptosis. Created in BioRender. Xia, S. (2024) https://BioRender.com/z40q507.

apoptotic AMs in an advanced sepsis-induced lung injury rat model, which partly explained reduced defenses in septic lungs, and also superimposed on the susceptibility of septic lungs.[40] Another study showed that relatively high dexamethasone doses induced AMs apoptosis in vitro, weakening lung immune functions and increasing secondary infection risks in patients.[41]

Apoptosis is a highly coordinated process that maintains tissue health by balancing cell proliferation or death. Although the mechanisms of apoptosis have been extensively studied, the link between apoptosis in AMs and various pathological states needs to be further explored. A more comprehensive analysis of the key molecules that play specific roles in ALI/ARDS is needed in the future to reveal the specific mechanisms and roles of apoptosis in AMs in these diseases.

AMs Pyroptosis in ALI

The Pyroptosis Pathway

Pyroptosis is a specific RCD widespread in several infectious and inflammatory respiratory diseases, including ALI, chronic obstructive pulmonary disease, and asthma.[42,43] Inflammatory vesicle complex assembly is a key step in cellular pyroptosis.[44] When a host is subjected to abnormal conditions, such as a microbial infection, stress, and/or tissue damage, pyroptosis is activated, which initiates a series of signaling cascades to activate the inflammasome, prompting inflammatory factor release from immune cells, and executing the effector protein gasdermin (GSDM)[45] (Figure 3). Although pyroptosis is initiated by different pathways, it is ultimately performed by the GSDM protein family, most of which share highly conserved N- and C-terminal structural domains (NTDs and CTDs, respectively).[46] NTDs are activated via CTD dissociations, which effectively solubilizes the phospholipid bilayer and forms pores in membranes, disrupting cellular membrane integrity and osmotic potential, leading to membrane rupture, chromatin condensation, and DNA fragmentation.[47,48] Thus, pyroptosis is defined as a GSDM-mediated regulated necrosis.

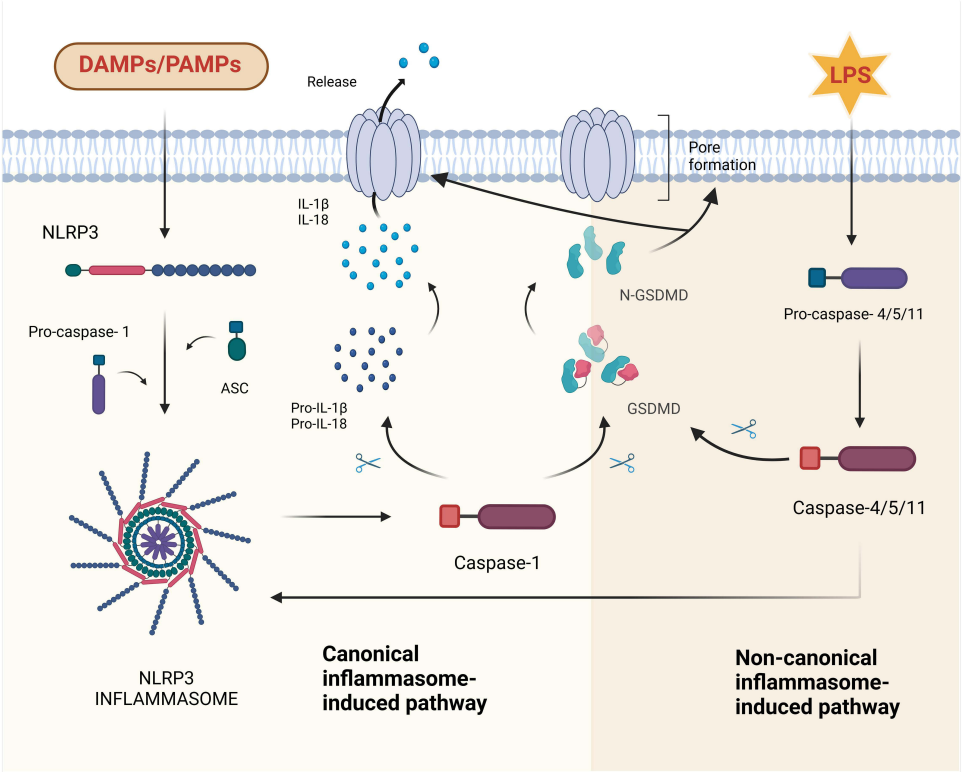

Figure 3 The canonical and non-canonical inflammasome pathways in pyroptosis. In the canonical pyroptosis pathway, active NLRP3 binds Pro-caspase-1 via ACS to form NLRP3 inflammasome, followed by activation of Caspase-1. Active Caspase-1 mediates the maturation and cleavage of IL-18 and IL-1β from the GSDMD, which forms membrane pores and releases cytoplasmic inflammatory contents, leading to cellular pyroptosis. In the non-canonical pyroptosis pathway, lipopolysaccharide (LPS) derived from Gram-negative bacteria directly activates Caspase-4/5/11. Activated Caspase-4/5/11 cleaves the GSDMD to induce pore formation, while activating the NLRP3 inflammasome through K efflux, leading to pyroptosis. Created in BioRender. Xia, S. (2024) https://BioRender.com/y83o292.

Pyroptosis in AMs

Elevated AMs-Mediated Pyroptosis Levels in ALI

A growing body of evidence now suggests that cellular pyroptosis has key roles in inflammatory responses to respiratory diseases. In particular, AMs pyroptosis, in response to intratracheal LPS administration, significantly enhances lung inflammation.[49] Elevated NLRP3, ASC, LI-1β, and IL-18 expression levels were identified in a severe sepsis-induced lung injury model, as well as higher GSDMD precursor and spliceosome levels in lung tissue.[50] NLRP3 inflammatory vesicle activation in AMs led to caspase-1 activation and IL-1β production, further exacerbating lung injury during mechanical ventilation in ALI patients.[51] Critically, the specific caspase-1 inhibitor Ac-YVAD-CMK prevents AMs-induced pyroptosis and lung injury.[49]

During in vitro cardiopulmonary bypass, NLRP3/ASC-mediated pyroptosis in AMs was shown to enhance High mobility group box 1 (HMGB1) secretion, thereby exacerbating pulmonary ischemia-reperfusion (I/R)-associated ALI.[52] HMGB1, in turn, mediated AMs activation via toll-like receptor 4 (TLR4).[53] Inhibited Nlrp3 inflammatory vesicles then attenuated AMs death and HMGB1 release from AMs, thereby alleviating lung inflammation.

Recent studies reported that interferon regulatory factor-1 (IRF-1) activated caspase-1-dependent pyroptosis and inflammatory factor release in AMs in a mechanical lung injury model.[54] In in vivo studies, Wu et al showed that IRF-1 deficiency inhibited pyroptosis in AMs during LPS-induced ALI and confirmed the importance of TLR4 signaling for IRF-1 expression and subsequent caspase-1 activation.[55]

Xu et al reported that LPS simultaneously induced pyrin expression by activating NLRP3 inflammasomes in AMs.[56] Pyrin acts as a PRR that triggers caspase-1 inflammasome assembly.[57] LPS mediates IL-10 up-regulation in AMs, which enhances pyrin expression in an autocrine manner and inhibits inflammasome activation, which may be a self-regulatory mechanism to alleviate inflammation. Hemorrhagic shock (HS) inhibits LPS-induced IL-10 expression, which in turn

decreases pyrin expression to promote inflammatory vesicle activation and increase IL-1β secretion in the lungs, leading to increased lung inflammation.[56]

AMs Affect Pyroptosis via TLR4/Myd88/NF-κB Signaling

He et al demonstrated that LPS-induced IL-1β release had a profound effect on AMs pyroptosis and lung inflammation development.[58] In AMs, LPS–TLR4 signaling activates NLRP3 inflammatory vesicles and releases IL-1β. Simultaneous IL-1 receptor I (IL-1RI) up-regulation on AMs surfaces via MyD88 and NF-κB dependent signaling was shown to sensitize AMs to IL-1β, which subsequently caused the formation of ASC pyroptosome and the amplification of the pyroptosis of the AMs, thereby exacerbating ALI.[58]

Myeloid differentiation protein 2 (MD-2) acts as a co-receptor for the classical TLR4 and regulates NLRP3 inflammatory vesicle activation and IL-1β secretion in LPS-treated AMs.[59] In AMs, MD-2 gene knockdown reduces LPS-induced increases in NLRP3, caspase-1 protein, and IL-1β secretion via MyD88/NF-κB signaling.[60]

AMs Pyroptosis Induction via the cGAS–STING Pathway

Growing evidence now suggests that NLRP3 inflammatory vesicle activation and pyroptosis are regulated by mitochondrial processes.[61] LPS-induced mitochondrial dysfunction and cytoplasmic mitochondrial DNA release triggered inflammatory responses upon cGAS–STING axis activation, and consequently activation of the interferon regulatory factor 3 (IRF3) or NF-κB pathway.[62] It has been mentally demonstrated that the cGAS-STING pathway may participate in LPS-induced ALI by regulating NLRP3 and macrophage pyroptosis.[63] Thus, activation of the cGAS-STING-IRF3 pathway is involved in the regulation of pyroptosis in AMs, which reveals a novel regulatory mechanism in AMs. A recent study suggested that 4-OI, a cell-permeable intrinsic clathrin derivative, may inhibit NLRP3 inflammatory vesicle activation in a STING–IRF3-dependent manner. Also, 4-OI pretreatment significantly inhibited up-regulated cGAS and STING protein expression, and TBK1 and IRF3 phosphorylation, both in vivo and in vitro, resulting in inhibition of NLRP3 inflammasome activation to ameliorate ARDS.[64] Thus, activation of the cGAS-STING-IRF3 pathway is involved in the regulation of pyroptosis in AMs, which reveals a novel regulatory mechanism in AMs.

AMs Pyroptosis is Regulated via Mitogen-Activated Protein Kinase (MAPK) Signaling

In ALI / ARDS, p38 MAPK signaling is activated, leading to significant increases in inflammatory factor expression levels.[65,66] p38 MAPK inhibitors significantly reduce NLRP3 inflammatory vesicle formation, decrease AMs pyroptosis and inflammatory factor release. Interestingly, more apoptosis was observed when p38 MAPK signaling was blocked. Therefore, p38 MAPK signaling blockade may induce a shift from pro- to non-inflammatory apoptosis in AMs, thereby alleviating ALI and preventing excessive inflammation.[67] Thus, balancing AMs pyroptosis and apoptosis may provide new therapeutic strategies for treating uncontrolled lung inflammation in patients with ALI/ARDS.

Extracellular Vesicles (EVs) Release from AMs During Pyroptosis Influence ALI Progression

Several new studies have reported that specific EVs are released during pyroptosis, which are key intercellular communication mediators involved in biological processes such as inflammation, immunomodulation, and tumorigenesis.[68,69] Micron-sized vesicles (1–5 μm) called pyroptotic bodies (PyrBDs) are formed during pyroptosis.[70] In early ALI stages, PyrBDs derived from pyroptotic AMs trigger exacerbated inflammatory responses. PyrBDs formation is dependent on caspase-1-mediated pyroptosis of AMs, and contain high Mitochondrial damage-associated molecular patterns (DAMPs) and inflammatory factors, such as TNF-α, IL-6, and IL-1β. These EVs promote epithelial cell activation via p38 MAPK signaling which induces interstitial vascular edema and facilitates neutrophil recruitment.[71] PyrBDs production is associated with inflammatory spread and requires more in-depth studies to examine their properties and functions.

Pyroptosis, an important component of innate immunity, plays a key role in fighting infection and responding to intrinsic danger signals. The current experiments found that pyroptosis of AMs exacerbated lung inflammation in ALI/ARDS, whereas inhibition of pyroptosis of AMs attenuated lung inflammation by reducing cellular and lung tissue damage and decreasing the expression of inflammatory factors. Given the critical role of AMs in maintaining lung

homeostasis, further investigation of the potential mechanism of AMs pyroptosis in acute lung injury and effective regulation of AMs pyroptosis maybe an effective clinical strategy to prevent or treat ALI.

AMs Necroptosis in ALI

The Necroptosis Pathway

Necroptosis is a newly discovered cell death type; it is mechanistically similar to apoptosis but morphologically similar to necrosis.[72,73] Necroptosis is activated as an alternative death pathway when cells undergo inflammatory, oxidative, or hypoxic stresses that prevent them from dying via apoptosis.[74] This process involves dead cell aggregation, cell membrane rupture, organelle swelling, cytoplasm and nucleus breakdown, and inflammatory vesicle formation.[75] Unlike apoptosis, necroptosis is generally regarded as a pro-inflammatory response and independent of cysteine asparaginase activity. Key factors in its regulation include receptor-interacting serine-threonine kinase 1 (RIPK1), RIPK3, and mixed-spectrum kinase structural domain-like proteins (MLKL)[76,77] (Figure 4).

Necroptosis in AMs

Increased AMs Necroptosis in ALI

It has been reported that RIPK3-mediated necrotizing apoptosis and inflammasome pathways are activated in ALI induced by LPS.[78] RIPK3-mediated necroptosis and inflammatory vesicle pathways are reportedly activated in LPS-induced ALI. Elevated RIPK3 levels may represent a ventilator-induced ALI marker.[79]

A recent important study reported that AMs specifically expressed high leptin receptor (Lepr) levels in several tissue-resident macrophages.[80] Lepr, as the receptor for the important metabolic hormone leptin, efficiently regulates plenary lipid quality, with high leptin levels associated with several immune and inflammatory disorders.[81] In AMs, Lepr-specific expression may be related to AMs roles degrading lipids to maintain surfactant homeostasis. Lepr signaling maintains lipid homeostasis in AMs and plasma membrane integrity, while inhibiting necroptosis by maintaining AMPK signaling,

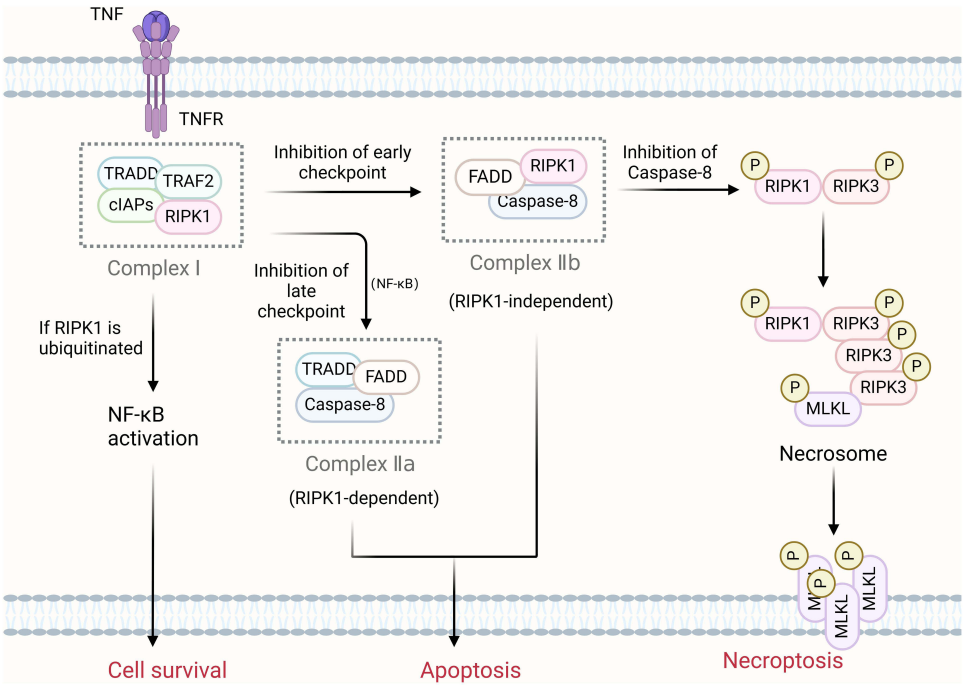

Figure 4 Necroptosis pathway. TNFα is the predominant upstream signalling component of necroptosis apoptosis.TNF-α activates TNFR1, which recruits scaffolding proteins TRADD, TRAF2, RIPK1 and cIAP1/2 to form plasma membrane-associated complex I. Linear ubiquitination stabilises complex I, which activates the NF-κB signalling pathway, leading to cell survival. When NF-κB is inhibited, complex IIa is activated, initiating apoptosis. Disruption of the signalling checkpoint early in cell survival leads to induction of complex IIb, which induces apoptosis via activated Caspase-8. When Caspase-8 is inhibited, phosphorylated RIPK1 and phosphorylated RIPK3 recruit and phosphorylate their substrate MLKL to form the necrosome complex. Activated MLKL oligomerises and migrates to the plasma membrane, thereby triggering necroptosis. Created in BioRender. Xia, S. (2024) https://BioRender.com/d66m064.

thereby limiting inflammatory cell content release (eg, IL-1α) and neutrophil recruitment, and also attenuating lung inflammation by regulating AMs metabolism.[80]

Recent studies have indicated that MLKL is also prominently expressed in AMs, in particular when compared with monocyte-derived macrophages. In LPS-induced ALI, Triggering receptors expressed on myeloid cell-1 (TREM-1) acts as a PRR that induces necroptosis in AMs. TREM-1 blockade attenuates MLKL expression in AMs, and TREM-1 blocker treatment attenuates septal lung thickening and alveolar congestion in ALI mice.[82] Also, the mechanistic target of Rapamycin (mTOR)-dependent mitochondrial fission underlies TREM-1-triggered necroptosis and inflammation, and is one of the conditions required for mitochondrial autophagy, which seems to suggest that TREM-1 may mediate the death of AMs from multiple pathways.[83]

Osteopontin (OPN) is a major regulator involved in cell death and immunity.[84] Wang et al reported that in mice with ALI caused by influenza virus infection, Osteopontin knockdown significantly reduced P-MLKL levels in AMs, which alleviated necroptosis levels and attenuated ALI.[85]

Alveolar macrophages necroptosis is an important factor in the enhancement of lung inflammation in patients with inflammatory respiratory diseases. There has been a steady advancement of research on necroptosis in AMs. Although necroptotic signalling pathways and induction mechanisms have been well documented, their specific mechanisms in ALI/ARDS and their effective role in AMs are still worth exploring. The blockade of necroptosis is expected to alleviate inflammatory respiratory diseases such as ALI, and studies targeting the blockade of RIPK1 have progressed, but more clinical trials are still needed to determine the feasibility of targeting necroptosis in therapy.

AMs Autophagic Death in ALI

The Autophagic Cell Death Pathway

Autophagy, as the primary intracellular degradation system, is a cell protective mechanism under unfavorable conditions (eg oxidative stress) and acts via the lysosomal degradation of dysfunctional/damaged proteins, organelles, and intracellular pathogens.[86,87] Excessive autophagy activation often leads to cell death or inhibits cell proliferation in an apoptosis-independent manner.[88,89] The Cell Death Nomenclature Committee has recognized autophagic cell death (ACD) as an independent "subprogram of cell death", whose mechanism is significantly different from traditional apoptosis and is highly dependent on the autophagic pathway (or its components).[90] ACD can be further subdivided into three modes: autophagy-associated (coexistence of autophagy and apoptosis or other cell death), autophagy-mediated (autophagy promoting apoptotic cell death or other cell death modalities) and autophagy-dependent (autophagy as a distinct cell death pathway independent of apoptosis or necroptosis).[91] Increasing evidence indicates that the autophagic mechanism plays a direct role in determining specific cell death patterns3.[92] Therefore, in the following content, we not only delve into ACD in macrophages (AMs) but also supplement the functional study of AMs autophagy in ALI/ARDS.

Three autophagy types exist: macroautophagy, microautophagy, and chaperone-mediated autophagy.[87,93] In micro-autophagy, cytoplasmic components are directly transported into lysosomes and cytosolic organelles by inducing lysosomal membrane invagination.[94] Chaperone-mediated autophagy, on the other hand, allows for the direct entry of target proteins across lysosomal membranes via the recognition of specific target protein sequences by lysosomal chaperone proteins, without vesicle formation.[95] Macroautophagy is the most prominent version; it wraps and transports cytoplasmic materials to the lysosome for degradation via double-membrane structures called autophagosomes[96,97] (Figure 5). The key step in classical macroautophagy induction is UNC-51-like kinase (ULK) complex activation, followed by downstream Autophagy-related protein (Atg) recruitment and modification to initiate the process.[98]

Autophagic Cell Death in AMs

In ALI, AMs Autophagy Levels are Elevated

The effects of autophagy on ALI/ARDS are variable and may be either protective or injurious, depending on the physiological context.[99] It was reported that autophagy-related gene (eg, Atg7, Atg5, and Atg4b) deletions significantly exacerbated ALI development in mice.[100] Many autophagy-related regulators such as LC3B-II, Beclin 1, p62, and mTOR

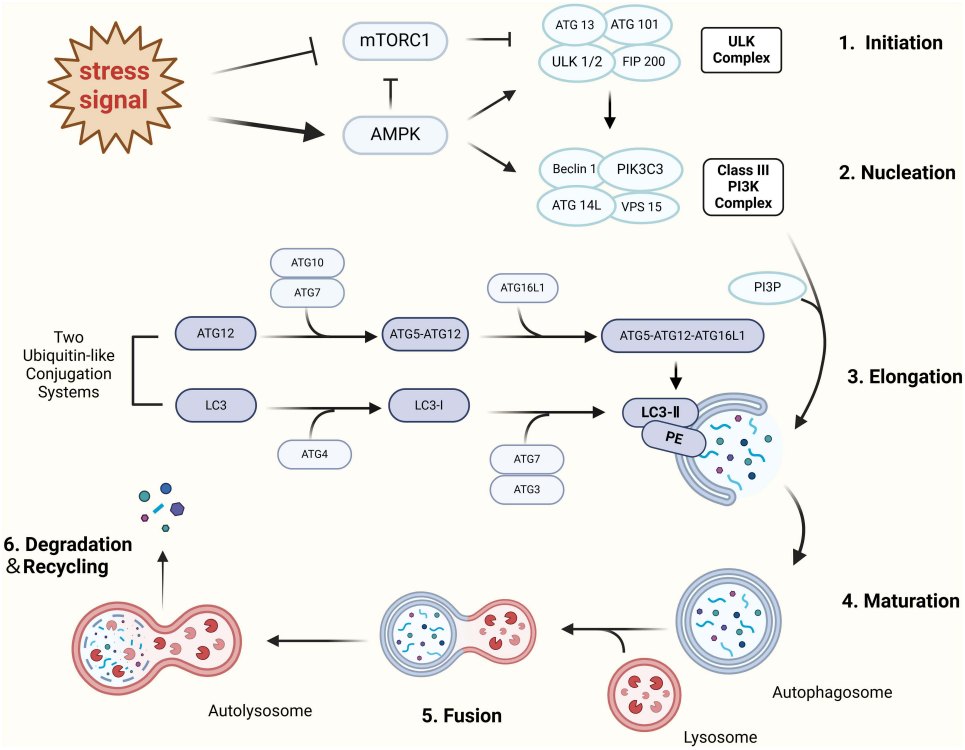

Figure 5 Classical autophagy pathway. In stress-induced macroautophagy, AMPK activation or inhibition of mTORC1 activity leads to the activation of the ULK complex and class III PI3K complex, resulting in the formation of phagocytic carriers. Two different ubiquitin-like coupling systems are involved in phagocytic carrier elongation: one involves ATG5-ATG12-ATG16L, and the other involves LC3-PE (LC3II), which helps to seal off double-membrane autophagosome formation. Eventually, autophagosomes fuse with lysosomes to form autophagic lysosomes for degradation. Created in BioRender. Xia, S. (2024) https://BioRender.com/i7111l42.

have key autophagy induction roles during lung injury.[101] A recent study found that Hydrogen-rich saline (HRS) regulated AMs polarization and inhibited apoptosis by inhibiting autophagy in rat AMs, thereby alleviating lung inflammation.[102] Thus, autophagy may impact ALI/ARDS progression by influencing AMs phenotypes and functions and helping regulate inflammatory responses.

It was previously shown that transforming growth factor-β-activated kinase-1 binding protein 2 (TAB2) interacted with the essential autophagy mediator Beclin-1 to regulate autophagy. Under different autophagy-inducing stimuli, TAB2 dissociated from Beclin1 and bound to TAK1, leading to downstream IKK/NF-κB signaling activation, thus allowing Beclin1 to initiate autophagy.[103] Another study also found that miR-155 overexpression inhibited TAB2 expression in AMs, induced autophagy, and reduced caspase-1 expression in cells and IL-1β and TNF-α levels in supernatants.[104] Thus, AMs autophagy may be activated by inhibiting TAB2 expression to reduce inflammation during septic lung injury.

The complement system functions as a first-line defense mechanism against pathogen invasion, and its activation product, C5a, directly activates neutrophils and macrophages and induces strong pro-inflammatory mediator expression.[105,106] Hu et al reported that in intestinal I/R-induced ALI, C5a activated AMs, as evidenced by MHC class II molecule expression and increased CD11b expression in AMs. Subsequent C5a binding to C5aR initiated Bcl-2 degradation and deregulated the inhibitory effects of Beclin-1, a key autophagy regulator, thereby increasing autophagy levels and inducing AMs apoptosis, which further contributed to ALI development. Critically, inhibited autophagy in AMs, using the autophagy inhibitor 3-Methyladenine or autophagy protein (Atg5) knockdown, largely prevented apoptosis.[107] Therefore, C5a-mediated autophagy in AMs induces but does not inhibit macrophage apoptosis, thereby increasing lung injury.

AMs Autophagy Attenuates ALI by Inhibiting NOD-Like Receptor (NLR) Protein Family Activity

Mitochondrial damage-associated molecular patterns (MTDs) occur due to mitochondrial rupture, are released into extracellular spaces during cell death, and are a major source of DAMPs.[108,109] MTDs induce NLRP3 inflammatory

vesicle activation, causing severe inflammatory responses in AMs, which leads to aseptic lung injury. Rapamycin-induced autophagy activation significantly reduces NLRP3 inflammasome activation in AMs stimulated by MTDs.[110]

Further studies also show that Up-regulated geranylgeranyl diphosphate synthase 1 (GGPPS1) was identified in a sepsis-induced lung injury mouse model and in MH-S cells stimulated with LPS.[111] GGPPS1 has important roles in several cellular processes such as cell growth, differentiation, proliferation, and protein trafficking.[112] GPPS1 depletion inhibits NLRP3 inflammasome activation by enhancing AMs autophagy, thereby attenuating sepsis-induced lung injury.[111]

Wen et al reported that HS, acting via HMGB1/TLR4 signaling, induced increased NOD2 expression in AMs, which enhanced lung inflammation. Additionally, up-regulated NOD2 signaling enhanced AMs autophagic activity, which in turn reduced NOD2 binding to RIP2 and inflammatory vesicle activation, thereby suppressing lung inflammation. This study also revealed that neutrophils were activated and migrated to alveolar spaces in the HS model, counteracting the anti-inflammatory effects of autophagy in AMs via Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent signaling, and enhancing lung inflammation after HS.[113] Notably, these findings highlight complex inter-cellular interactions underpinning ALI mechanisms.

AMs Autophagy Acts via MAPK and NF-κB Pathways

The release of injury-associated molecular patterns, such as HMGB1 and heat shock protein 60, is significantly increased during I/R injury.[114,115] In lung tissue, DAMPs bind to TLR4, triggering inflammatory cytokine production (including IL-1β and TNF) and activating AMs autophagy. In turn, autophagy promotes inflammatory responses activated by TLR4 signaling during lung I/R. TNF receptor-associated factor 6 (TRAF6) ubiquitination is inhibited when 3-methyladenine (autophagy inhibitor) or autophagy-related protein (Atg7 and BECN1) knockdown is used. Additionally, Atg7 knockdown reduced MAPK phosphorylation levels and NF-κB signaling activation markers in AMs, and also significantly reduced pro-inflammatory cytokine expression.[116] Thus, AMs autophagy is involved in TRAF6 ubiquitination in I/R-triggered ALI and has important roles in I/R injury-induced MAPK and NF-κB signaling activation and inflammatory responses.

Lipoproteins (LXs) are intrinsic anti-inflammatory lipid mediators synthesized in organisms via the arachidonic acid pathway.[117] Lipoxin A4 (LXA4) exerts protective effects against LPS-induced lung injury by inhibiting CCL2 secretion and release from resident macrophages, and reducing recruited macrophage and neutrophil accumulation.[118] Additionally, BML-111, an Lipoxin A4 receptor agonist, effectively inhibits MAPK1 and MAPK8 activation, thereby increasing AMs autophagy levels after LPS treatment, attenuating LPS-induced apoptosis, and decreasing pro-inflammatory factor levels in vivo.[119] Therefore, stimulating autophagy in AMs by targeting MAPK signaling may promote ALI regression.

AMs Autophagy Reduces Lung Injury by Modulating Endoplasmic Reticulum Stress (ERS)

Misfolded or immature protein accumulation in the endoplasmic reticulum (ER) lumen triggers a disease known as endoplasmic reticulum stress (ERS), which causes cellular damage and amplifies inflammatory responses.[120] Fan et al reported that extrinsic autophagy enhancement using rapamycin significantly reduced ERS protein marker levels (BIP, XBP-1, and CHOP) and the apoptosis-related marker caspase-3.[121] Another study demonstrated that the proteasome inhibitor MG132 elevated autophagy levels in hypoxia-reoxygenation (H/R)-treated cells, inhibited the ER/unfolded protein response stress pathway, and impeded apoptotic processes.[122] Thus, by attenuating ERS and oxidative stress in AMs, autophagy reduces apoptosis and thus preserves immune homeostasis in lung tissues.

AMs Autophagy Induction via the Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway is one of the most common pathways in inflammation and oxidative stress progression, and one of the major pathways activated by autophagy.[123] CoB1, a novel antimicrobial drug, reduced p21-Activated kinase 1 (PAK1) expression via a ubiquitination-mediated degradation pathway in a Pseudomonas aeruginosa-induced ALI model. This novel antimicrobial drug. PAK1 inhibition also reduced Akt1 phosphorylation levels, which led to Akt/mTOR signaling blockade and inhibited the ULK1/2-Atg13-FIP200 complex from undergoing autophagy precursor membrane translocation, thereby promoting AMs autophagy activation, cell survival, and bacterial clearance in AMs.[124]

Autophagy is a complex and dynamic process that plays different roles under different pathological conditions. In particular, targeted modulation of autophagy in AMs could be a strategy to address lung inflammation, but in-depth

studies on the specific mechanism of action of autophagy in AMs, how it is regulated, and its specific impacts (either benefits or harms) in the progression of acute lung injury (ALI) are still needed. Accordingly, there is a need to further elucidate the role and mechanisms of autophagy in acute lung injury in order to better utilise it for therapeutic purposes.

Crosstalk Between Different RCD Pathways in ALI/ARDS

In recent years, as RCD processes have become better understood, considerable attention has focused on the interactions (crosstalk) between different RCD modes. In an inflammatory disease context, multiple cell death types can be simultaneously induced, with interactions between the types influencing disease processes in a highly complex manner.[12,125] PANoptosis is a recently defined RCD type that may be triggered by interactions between AIM2, pyrin, and ZBP1, and incorporates key features of pyroptosis, apoptosis, and/or necroptosis.[126,127] PANoptosis manifestations are not explained by any of these three RCD pathways alone, suggesting interactions between RCD pathways. Additionally, ALI/ARDS is characterized by extensive inflammatory cell infiltration in lung tissue and excessive inflammatory responses, with neither apoptosis, pyroptosis, nor any of the other RCD types alone fully explaining the complex mechanisms underpinning the disease. These insights remind us that regulated and molecular crosstalk between RCD pathways dynamically influence ALI/ARDS progression.

Apoptosis and Autophagy

Autophagy and apoptosis pathways are interrelated as both appear to share common inducers and components. Both are affected by stimuli such as hypoxia, stress, and I/R, and share some key molecular regulators such as Bcl-2, p53, AKT, and mTOR.[128] Autophagy and apoptosis usually occur in the same cell, mainly where autophagy precedes apoptosis.[129] A previous study reported that autophagy and apoptosis had different roles at different stages in LPS-induced ALI. In early ALI phases, autophagy-dominated cell death patterns peaked within 2 hours, while in contrast, apoptosis gradually increased at later phases and peaked at 6 hours.[130]

In most cases, apoptosis and autophagy appear to inhibit each other. Autophagy provides a protective mechanism against apoptosis. Autophagy also reduces apoptosis in AMs by inhibiting caspase activation via attenuated ERS and oxidative stress.[121] In turn, activated apoptosis-associated proteins also inhibit autophagy by degrading autophagy-associated proteins. Atg3 degradation, induced by caspase-8 activation, was shown to restrict autophagic activity.[131] Beclin-1 is cleaved by caspase-8, thereby inhibiting autophagy.[132] In some special cases, autophagy supports apoptosis or assists apoptotic processes without causing cell death. Martyniszyn et al reported that autophagy and apoptosis occurred simultaneously in macrophages during later infection stages, and that autophagy may have assisted macrophage death by enhancing apoptosis.[133]

Apoptosis and Pyroptosis

Extensive interactions appear to occur between pyroptosis and apoptosis. In macrophages, GSDMD is the only caspase-1 substrate that induces pyroptosis, while in its absence, caspase-1-induced apoptosis triggers GSDMD-mediated secondary necroptosis/pyroptosis via the BID-caspase-9-caspase-3 axis.[134] In an ALI model, inhibited p38 MAPK signaling appeared to promote a shift in macrophage death patterns from pyroptosis to apoptosis, thereby attenuating lung inflammation.[67] Pro-inflammatory pyroptosis and non-inflammatory apoptosis are functionally distinct cellular responses, with the balance between them depending on the extent of the stimulus. Under intense stimulation, rapid pyroptosis predominates leading to neglect of the apoptotic response activated by inflammatory vesicles.[135]

Pyroptosis and Autophagy

Similar to apoptosis, autophagy may have key roles maintaining intracellular homeostasis by regulating pyroptosis. Numerous studies have reported interactions between NLRP3 inflammasomes and autophagy, with interrupted autophagy potentially causing over activated NLRP3 inflammasomes.[136,137] SESN2 is a stress-inducible protein that inhibits NLRP3 inflammasome activation in macrophages by inducing mitochondrial autophagy. Kim et al showed that in MTD-induced ALI, enhanced AMs autophagy inhibited NLRP3 inflammatory vesicle functions, thereby inhibiting caspase-1-mediated

pyroptosis signaling.[138] Therefore, autophagy may be viewed as a negative regulator of pyroptosis, with activated autophagy improving sepsis-associated ALI.

Pyroptosis and NETosis

As a novel RCD pathway, NETosis is a neutrophil death pathway characterized by the release of "neutrophil extracellular trapping networks" (NETs) composed of proteins which made of chromatin and intracellular granule bodies released by dead neutrophils.[139] A correlation was shown to exist between macrophage death and NET release. HMGB1 released from NETs promoted macrophage pyroptosis and inflammation in sepsis by forming inflammatory vesicles and activating caspase-1 via receptor for advanced glycation end products (RAGE) and dynamin-dependent signaling pathways.[140] Specific GSDMD deletion in neutrophils also prevented LPS-induced lung injury.[141] In an ALI/ARDS model, NETs directly promoted alveolar macrophage pyroptosis by activating AIM2 inflammatory vesicles, which enhanced neutrophil chemotaxis in the alveolar lumen and increased cytokine (IL-6, TNF-α, and IL-1β) concentrations in the alveoli, creating a vicious circle that may have contributed to a cytokine storm and exacerbated lung injury.[58,142]

Necroptosis, Pyroptosis, and Autophagy

Currently, studies examining interactions between pyroptosis, autophagy, and necroptosis are relatively limited. Kang et al reported that necroptosis directly or indirectly promoted inflammasome activation, and that the TLR3-mediated activation of of NLRP3 inflammasomes required RIPK3/MLKL activity.[143] Chen et al showed that RIPK3 and GSDMD signaling both amplified necroinflammation and tissue factor release in macrophages and endothelial cells, leading to tissue damage. RIPK3-mediated necrotic apoptosis and GSDMD-mediated pyroptosis both synergistically contributed to tissue injury during sepsis.[144] Mitochondrial fission is believed to be required for mitochondrial autophagy. A recent study demonstrated that TREM-1 activated mTOR-dependent mitochondrial fission, which in turn led to necrotic apoptosis in AMs, thereby exacerbating ALI.[82] Overall, pyroptosis and autophagy synergize with necrotic apoptosis to accelerate disease processes.

The Therapeutic Potential of Targeting RCD Pathways

Given the key impact of AMs regulated cell death on the progression of ALI/ARDS, the development of synthetic or natural products that can modulate key molecules in the cell death pathway is expected to become an effective strategy for treating this disease. Currently, Various RCD inhibitors have been developed, offering possibilities for further exploration of therapeutic strategies. The Bcl-2 inhibitor venetoclax alleviate ALI by increasing neutrophil apoptosis.[145] Similarly, RIPK1-targeting inhibitors of necrotizing apoptosis show significant protection during ALI and may be a strategy against COVID-19.[146] Matrine, a product purified from medicinal plants, can block ASC speck formation upon NLRP3 inflammasome activation, thereby inhibiting macrophage pyroptosis and increasing the survival rate of septic mice.[147] Currently, in some complex disease models, the simultaneous and multiple inhibition of RCD pathways may be beneficial in effectively alleviating inflammation and treating the disease.

Through in-depth study of the molecular mechanisms of RCD in Ams, we are hopeful to uncover new therapeutic targets for the prevention or treatment of ALI/ARDS, thereby improving patient survival rates and optimizing their prognosis. Additionally, these studies may enable us to tailor personalized treatment plans based on the unique pathophysiological characteristics of each patient, significantly enhancing the survival chances of ALI/ARDS patients. At the same time, these findings may also provide important therapeutic insights and strategies for other lung diseases that currently lack curative methods.

Despite the theoretical therapeutic potential of targeted interventions in AMs RCD pathways, many practical application challenges exist. First, due to overlapping RCD pathways, inhibitors targeting single pathways may have limited effects. The inhibition of one pathway may trigger aberrant activation of alternative RCD pathways and caspases. Additionally, some inhibitors (eg, MLKL inhibitors) carry cytotoxicity risks and may have off-target effects.[148] In an ALI/ARDS context, the regulatory mechanisms underpinning regulatory AMs death are highly complex, involving not only multiple signaling molecules and pathways, but also crosstalk between RCD pathways that can shift between synergy or inhibition due to different times, environments, and stimuli. Therefore, how do we precisely target specific

cellular and molecular pathways without affecting other important physiological processes? To answer this, future RCD pathway studies are required to identify overlapping processes and intersections. Additionally, the development of safe and effective interventions and appropriate drug delivery systems, ensuring therapeutic efficacy, is fundamental to achieving successful clinical outcomes.

Conclusions and Perspectives

Imbalanced AMs activation and function may lead to dysregulated immune responses and lung disease development. During inflammatory diseases, AMs intervene via several mechanisms, of which RCD pathway activation is decisive in maintaining lung homeostasis and modulating inflammation. Elevated apoptosis levels help AMs remove damaged cells and prevent excessive inflammation spread.[25] However, AMs apoptosis may decrease effective immune cell functions and promote lung inflammation.[40,41] Activated AMs pyroptosis exacerbates lung injury by activating inflammatory vesicles and inflammatory factor release.[149] AMs autophagy removes detrimental inflammatory factors from the body and attenuates oxidative stress levels, resulting in protective effects.[110,111,121] However, over-activated autophagy can lead to AMs dysfunction, thereby exacerbating lung injury.[107,116] Necroptosis promotes inflammation, but its mechanisms in AMs remain unexplored.[150] We now understand that crosstalk between different RCD types is both complex and flexible, especially during ALI/ARDS. Interactions between RCD pathways depend on cell type, the stimulus, and environmental conditions. Different RCD pathways may simultaneously occur because they share similar components. When one mode of death is inhibited, other replacement apoptosis mechanism can be triggered.[151,152] Thus, targeting RCD pathways is a potential strategy in treating lung injury.

Translational and clinical studies examining regulatory death mechanisms in AMs are scarce, with most basic research on RCD effects in lung disease focusing on alveolar epithelial cells, endothelial cells, and in a broader sense, macrophages. In recent years, there are still many unknowns in RCD of AMs research have been identified, such as ferroptosis, parthanatos, and lysosome-dependent cell death, which have not been the focus of this review. We anticipate that future studies will address these knowledge gaps. However, some studies have demonstrated the unique performance of AMs in RCD pathways, which confirms the considerable research potential in this area. Additionally, ALI/ARDS disease processes are rapid and variable, and identifying which RCD pathways are predominant at different stages will be critical when determining precision and personalized therapies.

In conclusion, we must focus on AMs roles in maintaining healthy lung homeostasis and how they affect inflammatory responses and tissue repair via RCD pathways in pathological states. This strategy should provide new concepts for treating ALI/ARDS and other lung disease.

Acknowledgments

We appreciate the linguistic support provided by BioMed Proofreading LLC (http://www.biomedproofreading.com) in the writing of this paper.

Author Contributions

All authors have made significant contributions to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by Hangzhou Science and Technology Bureau (20231203A06).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Matuschak GM, Lechner AJ. Acute lung injury and the acute respiratory distress syndrome: pathophysiology and treatment. *Mo Med*. 2010;107(4):252–258.
2. Mokra D, Kosutova P. Biomarkers in acute lung injury. *Respir Physiol Neurobiol*. 2015;209:52–58. doi:10.1016/j.resp.2014.10.006
3. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet*. 2021;398(10300):622–637. doi:10.1016/S0140-6736(21)00439-6
4. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. *Cell Res*. 2019;29(5):347–364. doi:10.1038/s41422-019-0164-5
5. Vitale I, Pietrocola F, Guilbaud E, et al. Apoptotic cell death in disease-current understanding of the NCCD 2023. *Cell Death Differ*. 2023;30(5):1097–1154. doi:10.1038/s41418-023-01153-w
6. Qi X, Luo Y, Xiao M, et al. Mechanisms of alveolar type 2 epithelial cell death during acute lung injury. *Stem Cells*. 2023;41(12):1113–1132. doi:10.1093/stmcls/sxad074
7. Ma A, Feng Z, Li Y, et al. Ferroptosis-related signature and immune infiltration characterization in acute lung injury/acute respiratory distress syndrome. *Respir Res*. 2023;24(1):154. doi:10.1186/s12931-023-02429-y
8. Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation. *Respir Res*. 2018;19(1):50. doi:10.1186/s12931-018-0756-5
9. Doitsh G, Cavrois M, Lassen KG, et al. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. *Cell*. 2010;143(5):789–801. doi:10.1016/j.cell.2010.11.001
10. Arora S, Dev K, Agarwal B, Das P, Syed MA. Macrophages: their role, activation and polarization in pulmonary diseases. *Immunobiology*. 2018;223(4–5):383–396. doi:10.1016/j.imbio.2017.11.001
11. Tang PS, Mura M, Seth R, Liu M. Acute lung injury and cell death: how many ways can cells die? *Am J Physiol Lung Cell Mol Physiol*. 2008;294(4):L632–641. doi:10.1152/ajplung.00262.2007
12. Linkermann A, Stockwell BR, Krautwald S, Anders HJ. Regulated cell death and inflammation: an auto-amplification loop causes organ failure. *Nat Rev Immunol*. 2014;14(11):759–767. doi:10.1038/nri3743
13. Shotland AM, Fontenot AP, McKee AS. Pulmonary macrophage cell death in lung health and disease. *Am J Respir Cell Mol Biol*. 2021;64(5):547–556. doi:10.1165/rcmb.2020-0420TR
14. Murphy J, Summer R, Wilson AA, Kotton DN, Fine A. The prolonged life-span of alveolar macrophages. *Am J Respir Cell Mol Biol*. 2008;38(4):380–385. doi:10.1165/rcmb.2007-0224RC
15. Laskin DL, Weinberger B, Laskin JD. Functional heterogeneity in liver and lung macrophages. *J Leukoc Biol*. 2001;70(2):163–170. doi:10.1189/jlb.70.2.163
16. Lavin Y, Mortha A, Rahman A, Merad M. Regulation of macrophage development and function in peripheral tissues. *Nat Rev Immunol*. 2015;15(12):731–744. doi:10.1038/nri3920
17. Aegerter H, Lambrecht BN, Jakubzick CV. Biology of lung macrophages in health and disease. *Immunity*. 2022;55(9):1564–1580. doi:10.1016/j.immuni.2022.08.010
18. Murray PJ. Macrophage polarization. *Annu Rev Physiol*. 2017;79:541–566. doi:10.1146/annurev-physiol-022516-034339
19. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol*. 2008;8(12):958–969. doi:10.1038/nri2448
20. Bissonnette EY, Lauzon-Joset JF, Debley JS, Ziegler SF. Cross-talk between alveolar macrophages and lung epithelial cells is essential to maintain lung homeostasis. *Front Immunol*. 2020;11:583042. doi:10.3389/fimmu.2020.583042
21. Mould KJ, Barthel L, Mohning MP, et al. Cell origin dictates programming of resident versus recruited macrophages during acute lung injury. *Am J Respir Cell Mol Biol*. 2017;57(3):294–306. doi:10.1165/rcmb.2017-0061OC
22. Roberts AW, Lee BL, Deguine J, John S, Shlomchik MJ, Barton GM. Tissue-resident macrophages are locally programmed for silent clearance of apoptotic cells. *Immunity*. 2017;47(5):913–927.e916. doi:10.1016/j.immuni.2017.10.006
23. Galani V, Tatsaki E, Bai M, et al. The role of apoptosis in the pathophysiology of Acute Respiratory Distress Syndrome (ARDS): an up-to-date cell-specific review. *Pathol Res Pract*. 2010;206(3):145–150. doi:10.1016/j.prp.2009.12.002
24. McCubbrey AL, Curtis JL. Efferocytosis and lung disease. *Chest*. 2013;143(6):1750–1757. doi:10.1378/chest.12-2413
25. Mahida RY, Scott A, Parekh D, et al. Acute respiratory distress syndrome is associated with impaired alveolar macrophage efferocytosis. *Eur Respir J*. 2021;58(3):2100829. doi:10.1183/13993003.00829-2021
26. Lambrecht BN. Alveolar macrophage in the driver's seat. *Immunity*. 2006;24(4):366–368. doi:10.1016/j.immuni.2006.03.008
27. Holt PG, Strickland DH, Wikström ME, Jahnsen FL. Regulation of immunological homeostasis in the respiratory tract. *Nat Rev Immunol*. 2008;8(2):142–152. doi:10.1038/nri2236
28. Liu C, Xiao K, Xie L. Progress in preclinical studies of macrophage autophagy in the regulation of ALI/ARDS. *Front Immunol*. 2022;13:922702. doi:10.3389/fimmu.2022.922702
29. Tan S, Yang S, Chen M, et al. Lipopolysaccharides promote pulmonary fibrosis in silicosis through the aggravation of apoptosis and inflammation in alveolar macrophages. *Open Life Sci*. 2020;15(1):598–605. doi:10.1515/biol-2020-0061
30. Wei X, Yi X, Liu J, et al. Circ-phkb promotes cell apoptosis and inflammation in LPS-induced alveolar macrophages via the TLR4/MyD88/NF-kB/CCL2 axis. *Respir Res*. 2024;25(1):62. doi:10.1186/s12931-024-02677-6
31. Liu B, He R, Zhang L, et al. Inflammatory caspases drive pyroptosis in acute lung injury. *Front Pharmacol*. 2021;12:631256. doi:10.3389/fphar.2021.631256
32. Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat Rev Mol Cell Biol*. 2019;20(3):175–193. doi:10.1038/s41580-018-0089-8
33. Lossi L. The concept of intrinsic versus extrinsic apoptosis. *Biochem J*. 2022;479(3):357–384. doi:10.1042/BCJ20210854
34. Li H, Zhu H, Xu CJ, Yuan J. Cleavage of Bid by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell*. 1998;94(4):491–501. doi:10.1016/S0092-8674(00)81590-1
35. Humphreys L, Espona-Fiedler M, Longley DB. FLIP as a therapeutic target in cancer. *Febs J*. 2018;285(22):4104–4123. doi:10.1111/febs.14523

36. Gajate C, Gonzalez-Camacho F, Mollinedo F. Lipid raft connection between extrinsic and intrinsic apoptotic pathways. *Biochem Biophys Res Commun*. 2009;380(4):780–784. doi:10.1016/j.bbrc.2009.01.147
37. Bao X, Zhang Q, Liu N, et al. Characteristics of circular RNA expression of pulmonary macrophages in mice with sepsis-induced acute lung injury. *J Cell Mol Med*. 2019;23(10):7111–7115. doi:10.1111/jcmm.14577
38. Li B, Zhang H, Zeng M, et al. Bone marrow mesenchymal stem cells protect alveolar macrophages from lipopolysaccharide-induced apoptosis partially by inhibiting the Wnt/β-catenin pathway. *Cell Biol Int*. 2015;39(2):192–200. doi:10.1002/cbin.10359
39. Yang L, Zhang Z, Zhuo Y, et al. Resveratrol alleviates sepsis-induced acute lung injury by suppressing inflammation and apoptosis of alveolar macrophage cells. *Am J Transl Res*. 2018;10(7):1961–1975.
40. Lu MC, Liu TA, Lee MR, Lin L, Chang WC. Apoptosis contributes to the decrement in numbers of alveolar macrophages from rats with polymicrobial sepsis. *J Microbiol Immunol Infect*. 2002;35(2):71–77.
41. Zeng S, Qiao H, Lv XW, Fan D, Liu T, Xie D. High-dose dexamethasone induced LPS-stimulated rat alveolar macrophages apoptosis. *Drug Des Devel Ther*. 2017;11:3097–3104. doi:10.2147/DDDT.S147014
42. Sun J, Li Y. Pyroptosis and respiratory diseases: a review of current knowledge. *Front Immunol*. 2022;13:920464. doi:10.3389/fimmu.2022.920464
43. Feng Y, Li M, Yangzhong X, et al. Pyroptosis in inflammation-related respiratory disease. *J Physiol Biochem*. 2022;78(4):721–737. doi:10.1007/s13105-022-00909-1
44. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med*. 2015;21(7):677–687. doi:10.1038/nm.3893
45. Kuriakose T, Kanneganti TD. Pyroptosis in antiviral immunity. *Curr Top Microbiol Immunol*. 2023;442:65–83. doi:10.1007/82_2019_189
46. Zou J, Zheng Y, Huang Y, Tang D, Kang R, Chen R. The versatile gasdermin family: their function and roles in diseases. *Front Immunol*. 2021;12:751533. doi:10.3389/fimmu.2021.751533
47. Kovacs SB, Miao EA. Gasdermins: effectors of pyroptosis. *Trends Cell Biol*. 2017;27(9):673–684. doi:10.1016/j.tcb.2017.05.005
48. Sborgi L, Rühl S, Mulvihill E, et al. GSDMD membrane pore formation constitutes the mechanism of pyroptotic cell death. *EMBO J*. 2016;35(16):1766–1778. doi:10.15252/embj.201694696
49. Wu DD, Pan PH, Liu B, et al. Inhibition of alveolar macrophage pyroptosis reduces lipopolysaccharide-induced acute lung injury in mice. *Chin Med J*. 2015;128(19):2638–2645. doi:10.4103/0366-6999.166039
50. Wang YC, Liu QX, Zheng Q, et al. Dihydromyricetin alleviates sepsis-induced acute lung injury through inhibiting NLRP3 inflammasome-dependent pyroptosis in mice model. *Inflammation*. 2019;42(4):1301–1310. doi:10.1007/s10753-019-00990-7
51. Jones HD, Crother TR, Gonzalez-Villalobos RA, et al. The NLRP3 inflammasome is required for the development of hypoxemia in LPS/mechanical ventilation acute lung injury. *Am J Respir Cell Mol Biol*. 2014;50(2):270–280. doi:10.1165/rcmb.2013-0087OC
52. Hou L, Yang Z, Wang Z, et al. NLRP3/ASC-mediated alveolar macrophage pyroptosis enhances HMGB1 secretion in acute lung injury induced by cardiopulmonary bypass. *Lab Invest*. 2018;98(8):1052–1064. doi:10.1038/s41374-018-0073-0
53. Deng Y, Yang Z, Gao Y, et al. Toll-like receptor 4 mediates acute lung injury induced by high mobility group box-1. *PLoS One*. 2013;8(5):e64375. doi:10.1371/journal.pone.0064375
54. Dai M, Li Q, Pan P, Giovarelli M. The modulation of interferon regulatory Factor-1 via Caspase-1-mediated alveolar macrophage pyroptosis in ventilator-induced lung injury. *Mediators Inflamm*. 2022;2022:1002582. doi:10.1155/2022/1002582
55. Wu D, Pan P, Su X, et al. Interferon regulatory factor-1 mediates alveolar macrophage pyroptosis during LPS-induced acute lung injury in mice. *Shock*. 2016;46(3):329–338. doi:10.1097/SHK.0000000000000595
56. Xu P, Wen Z, Shi X, et al. Hemorrhagic shock augments Nlrp3 inflammasome activation in the lung through impaired pyrin induction. *J Immunol*. 2013;190(10):5247–5255. doi:10.4049/jimmunol.1203182
57. Xu H, Yang J, Gao W, et al. Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. *Nature*. 2014;513(7517):237–241.
58. He X, Qian Y, Li Z, et al. TLR4-upregulated IL-1β and IL-1RI promote alveolar macrophage pyroptosis and lung inflammation through an autocrine mechanism. *Sci Rep*. 2016;6(1):31663. doi:10.1038/srep31663
59. Visintin A, Mazzoni A, Spitzer JA, Segal DM. Secreted MD-2 is a large polymeric protein that efficiently confers lipopolysaccharide sensitivity to toll-like receptor 4. *Proc Natl Acad Sci U S A*. 2001;98(21):12156–12161. doi:10.1073/pnas.211445098
60. Luo M, Hu L, Li D, et al. MD-2 regulates LPS-induced NLRP3 inflammasome activation and IL-1beta secretion by a MyD88/NF-κB-dependent pathway in alveolar macrophages cell line. *Mol Immunol*. 2017;90:1–10. doi:10.1016/j.molimm.2017.06.035
61. Liu Q, Zhang D, Hu D, Zhou X, Zhou Y. The role of mitochondria in NLRP3 inflammasome activation. *Mol Immunol*. 2018;103:115–124. doi:10.1016/j.molimm.2018.09.010
62. West AP, Khoury-Hanold W, Staron M, et al. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature*. 2015;520(7548):553–557. doi:10.1038/nature14156
63. Ning L, Wei W, Wenyang J, Rui X, Qing G. Cytosolic DNA-STING-NLRP3 axis is involved in murine acute lung injury induced by lipopolysaccharide. *Clin Transl Med*. 2020;10(7):e228. doi:10.1002/ctm2.228
64. Wu YT, Xu WT, Zheng L, et al. 4-octyl itaconate ameliorates alveolar macrophage pyroptosis against ARDS via rescuing mitochondrial dysfunction and suppressing the cGAS/STING pathway. *Int Immunopharmacol*. 2023;118:110104. doi:10.1016/j.intimp.2023.110104
65. Li W, Li D, Chen Y, et al. Classic signaling pathways in alveolar injury and repair involved in sepsis-induced ALI/ARDS: new research progress and prospect. *Dis Markers*. 2022;2022:6362344. doi:10.1155/2022/6362344
66. Tirunavalli SK, Gourishetti K, Kotipalli RSS, et al. Dehydrozingerone ameliorates Lipopolysaccharide induced acute respiratory distress syndrome by inhibiting cytokine storm, oxidative stress via modulating the MAPK/NF-κB pathway. *Phytomedicine*. 2021;92:153729. doi:10.1016/j.phymed.2021.153729
67. Li D, Ren W, Jiang Z, Zhu L. Regulation of the NLRP3 inflammasome and macrophage pyroptosis by the p38 MAPK signaling pathway in a mouse model of acute lung injury. *Mol Med Rep*. 2018;18(5):4399–4409. doi:10.3892/mmr.2018.9427
68. Cypryk W, Nyman TA, Matikainen S. From inflammasome to exosome-does extracellular vesicle secretion constitute an inflammasome-dependent immune response? *Front Immunol*. 2018;9:2188. doi:10.3389/fimmu.2018.02188

69. Qu Y, Franchi L, Nunez G, Dubyak GR. Nonclassical IL-1 beta secretion stimulated by P2X7 receptors is dependent on inflammasome activation and correlated with exosome release in murine macrophages. *J Immunol*. 2007;179(3):1913–1925. doi:10.4049/jimmunol.179.3.1913
70. Lee H, Abston E, Zhang D, Rai A, Jin Y. Extracellular vesicle: an emerging mediator of intercellular crosstalk in lung inflammation and injury. *Front Immunol*. 2018;9:924. doi:10.3389/fimmu.2018.00924
71. Qin X, Zhou Y, Jia C, et al. Caspase-1-mediated extracellular vesicles derived from pyroptotic alveolar macrophages promote inflammation in acute lung injury. *Int J Biol Sci*. 2022;18(4):1521–1538. doi:10.7150/ijbs.66477
72. Galluzzi L, Kepp O, Chan FK, Kroemer G. Necroptosis: mechanisms and relevance to disease. *Annu Rev Pathol*. 2017;12:103–130. doi:10.1146/annurev-pathol-052016-100247
73. Dhuriya YK, Sharma D. Necroptosis: a regulated inflammatory mode of cell death. *J Neuroinflammation*. 2018;15(1):199. doi:10.1186/s12974-018-1235-0
74. Chen D, Yu J, Zhang L. Necroptosis: an alternative cell death program defending against cancer. *Biochim Biophys Acta*. 2016;1865(2):228–236. doi:10.1016/j.bbcan.2016.03.003
75. Zhou W, Yuan J. SnapShot: necroptosis. *Cell*. 2014;158(2):464–464.e461. doi:10.1016/j.cell.2014.06.041
76. Horne CR, Samson AL, Murphy JM. The web of death: the expanding complexity of necroptotic signaling. *Trends Cell Biol*. 2023;33(2):162–174. doi:10.1016/j.tcb.2022.05.008
77. Seo J, Nam YW, Kim S, Oh DB, Song J. Necroptosis molecular mechanisms: recent findings regarding novel necroptosis regulators. *Exp Mol Med*. 2021;53(6):1007–1017. doi:10.1038/s12276-021-00634-7
78. Chen J, Wang S, Fu R, et al. RIP3 dependent NLRP3 inflammasome activation is implicated in acute lung injury in mice. *J Transl Med*. 2018;16(1):233. doi:10.1186/s12967-018-1606-4
79. Siempos MKC II, Imamura M, Imamura M, et al. RIPK3 mediates pathogenesis of experimental ventilator-induced lung injury. *JCI Insight*. 2018;3(9). doi:10.1172/jci.insight.97102
80. Guo Z, Yang H, Zhang JR, Zeng W, Hu X. Leptin receptor signaling sustains metabolic fitness of alveolar macrophages to attenuate pulmonary inflammation. *Sci Adv*. 2022;8(28):eabo3064. doi:10.1126/sciadv.abo3064
81. Abella V, Scotece M, Conde J, et al. Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nat Rev Rheumatol*. 2017;13(2):100–109. doi:10.1038/nrrheum.2016.209
82. Zhong WJ, Zhang J, Duan JX, et al. TREM-1 triggers necroptosis of macrophages through mTOR-dependent mitochondrial fission during acute lung injury. *J Transl Med*. 2023;21(1):179. doi:10.1186/s12967-023-04027-4
83. Quiles JM, Gustafsson ÅB. The role of mitochondrial fission in cardiovascular health and disease. *Nat Rev Cardiol*. 2022;19(11):723–736. doi:10.1038/s41569-022-00703-y
84. Leavenworth JW, Verbinnen B, Wang Q, Shen E, Cantor H. Intracellular osteopontin regulates homeostasis and function of natural killer cells. *Proc Natl Acad Sci U S A*. 2015;112(2):494–499. doi:10.1073/pnas.1423011112
85. Wang J, Li X, Wang Y, Li Y, Shi F, Diao H. Osteopontin aggravates acute lung injury in influenza virus infection by promoting macrophages necroptosis. *Cell Death Discov*. 2022;8(1):97. doi:10.1038/s41420-022-00904-x
86. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. *Cell*. 2011;147(4):728–741. doi:10.1016/j.cell.2011.10.026
87. Kwon J, Kim J, Kim KI. Crosstalk between endoplasmic reticulum stress response and autophagy in human diseases. *Anim Cells Syst*. 2023;27(1):29–37. doi:10.1080/19768354.2023.2181217
88. Ryter SW, Mizumura K, Choi AM. The impact of autophagy on cell death modalities. *Int J Cell Biol*. 2014;2014:502676. doi:10.1155/2014/502676
89. Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. *Cell Death Differ*. 2015;22(3):367–376. doi:10.1038/cdd.2014.143
90. Galluzzi L, Vitale I, Abrams JM, et al. Molecular definitions of cell death subroutines: recommendations of the nomenclature committee on cell death 2012. *Cell Death Differ*. 2012;19(1):107–120. doi:10.1038/cdd.2011.96
91. Denton D, Kumar S. Autophagy-dependent cell death. *Cell Death Differ*. 2019;26(4):605–616. doi:10.1038/s41418-018-0252-y
92. Napoletano F, Baron O, Vandenabeele P, Mollereau B, Fanto M. Intersections between regulated cell death and autophagy. *Trends Cell Biol*. 2019;29(4):323–338. doi:10.1016/j.tcb.2018.12.007
93. Santambrogio L, Cuervo AM. Chasing the elusive mammalian microautophagy. *Autophagy*. 2011;7(6):652–654. doi:10.4161/auto.7.6.15287
94. Oku M, Sakai Y. Three distinct types of microautophagy based on membrane dynamics and molecular machineries. *Bioessays*. 2018;40(6):e1800008. doi:10.1002/bies.201800008
95. Mizushima N, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. *Annu Rev Cell Dev Biol*. 2011;27:107–132. doi:10.1146/annurev-cellbio-092910-154005
96. Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. *J Pathol*. 2010;221(1):3–12. doi:10.1002/path.2697
97. Wong AS, Cheung ZH, Ip NY. Molecular machinery of macroautophagy and its deregulation in diseases. *Biochim Biophys Acta*. 2011;1812(11):1490–1497. doi:10.1016/j.bbadis.2011.07.005
98. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol*. 2011;13(2):132–141. doi:10.1038/ncb2152
99. Wang K, Chen Y, Zhang P, Lin P, Xie N, Wu M. Protective features of autophagy in pulmonary infection and inflammatory diseases. *Cells*. 2019;8(2):1.
100. Aggarwal S, Mannam P, Zhang J. Differential regulation of autophagy and mitophagy in pulmonary diseases. *Am J Physiol Lung Cell Mol Physiol*. 2016;311(2):L433–452. doi:10.1152/ajplung.00128.2016
101. Vishnupriya S, Priya Dharshini LC, Sakthivel KM, Rasmi RR. Autophagy markers as mediators of lung injury-implication for therapeutic intervention. *Life Sci*. 2020;260:118308. doi:10.1016/j.lfs.2020.118308
102. Qiu P, Liu Y, Chen K, Dong Y, Liu S, Zhang J. Hydrogen-rich saline regulates the polarization and apoptosis of alveolar macrophages and attenuates lung injury via suppression of autophagy in septic rats. *Ann Transl Med*. 2021;9(12):974. doi:10.21037/atm-21-2489
103. Criollo A, Niso-Santano M, Malik SA, et al. Inhibition of autophagy by TAB2 and TAB3. *EMBO J*. 2011;30(24):4908–4920. doi:10.1038/emboj.2011.413

104. Liu F, Nie C, Zhao N, et al. MiR-155 alleviates septic lung injury by inducing autophagy via inhibition of transforming growth factor-β-activated binding protein 2. *Shock*. 2017;48(1):61–68. doi:10.1097/SHK.0000000000000839
105. Sun L, Guo RF, Gao H, Sarma JV, Zetoune FS, Ward PA. Attenuation of IgG immune complex-induced acute lung injury by silencing C5aR in lung epithelial cells. *FASEB J*. 2009;23(11):3808–3818. doi:10.1096/fj.09-133694
106. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. *Nat Immunol*. 2010;11(9):785–797. doi:10.1038/ni.1923
107. Hu R, Chen ZF, Yan J, et al. Complement C5a exacerbates acute lung injury induced through autophagy-mediated alveolar macrophage apoptosis. *Cell Death Dis*. 2014;5(7):e1330. doi:10.1038/cddis.2014.274
108. Tolle LB, Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. *J Pathol*. 2013;229(2):145–156. doi:10.1002/path.4124
109. Cloonan SM, Choi AM. Mitochondria in lung disease. *J Clin Invest*. 2016;126(3):809–820. doi:10.1172/JCI81113
110. Peng W, Peng F, Lou Y, et al. Autophagy alleviates mitochondrial DAMP-induced acute lung injury by inhibiting NLRP3 inflammasome. *Life Sci*. 2021;265:118833. doi:10.1016/j.lfs.2020.118833
111. Li D, Li C, Wang T, et al. Geranylgeranyl diphosphate synthase 1 knockdown suppresses NLRP3 inflammasome activity via promoting autophagy in sepsis-induced acute lung injury. *Int Immunopharmacol*. 2021;100:108106. doi:10.1016/j.intimp.2021.108106
112. Jeong A, Suazo KF, Wood WG, Distefano MD, Li L. Isoprenoids and protein prenylation: implications in the pathogenesis and therapeutic intervention of Alzheimer's disease. *Crit Rev Biochem Mol Biol*. 2018;53(3):279–310. doi:10.1080/10409238.2018.1458070
113. Wen Z, Fan L, Li Y, et al. Neutrophils counteract autophagy-mediated anti-inflammatory mechanisms in alveolar macrophage: role in posthemorrhagic shock acute lung inflammation. *J Immunol*. 2014;193(9):4623–4633. doi:10.4049/jimmunol.1400899
114. Tian Y, Charles EJ, Yan Z, et al. The myocardial infarct-exacerbating effect of cell-free DNA is mediated by the high-mobility group box 1-receptor for advanced glycation end products-Toll-like receptor 9 pathway. *J Thorac Cardiovasc Surg*. 2019;157(6):2256–2269.e2253. doi:10.1016/j.jtcvs.2018.09.043
115. van Golen RF, Reiniers MJ, Olthof PB, van Gulik TM, Heger M. Sterile inflammation in hepatic ischemia/reperfusion injury: present concepts and potential therapeutics. *J Gastroenterol Hepatol*. 2013;28(3):394–400. doi:10.1111/jgh.12072
116. Liu X, Cao H, Li J, et al. Autophagy induced by DAMPs facilitates the inflammation response in lungs undergoing ischemia-reperfusion injury through promoting TRAF6 ubiquitination. *Cell Death Differ*. 2017;24(4):683–693. doi:10.1038/cdd.2017.1
117. Chandrasekharan JA, Sharma-Walia N. Lipoxins: nature's way to resolve inflammation. *J Inflamm Res*. 2015;8:181–192. doi:10.2147/JIR.S90380
118. Mei HX, Ye Y, Xu HR, et al. LXA4 inhibits lipopolysaccharide-induced inflammatory cell accumulation by resident macrophages in mice. *J Inflamm Res*. 2021;14:1375–1385. doi:10.2147/JIR.S301292
119. Liu H, Zhou K, Liao L, Zhang T, Yang M, Sun C. Lipoxin A4 receptor agonist BML-111 induces autophagy in alveolar macrophages and protects from acute lung injury by activating MAPK signaling. *Respir Res*. 2018;19(1):243. doi:10.1186/s12931-018-0937-2
120. Kim I, Xu W, Reed JC. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat Rev Drug Discov*. 2008;7(12):1013–1030. doi:10.1038/nrd2755
121. Fan T, Chen L, Huang Z, et al. Autophagy decreases alveolar macrophage apoptosis by attenuating endoplasmic reticulum stress and oxidative stress. *Oncotarget*. 2016;7(52):87206–87218. doi:10.18632/oncotarget.13560
122. Fan T, Huang Z, Wang W, et al. Proteasome inhibition promotes autophagy and protects from endoplasmic reticulum stress in rat alveolar macrophages exposed to hypoxia-reoxygenation injury. *J Cell Physiol*. 2018;233(10):6748–6758. doi:10.1002/jcp.26516
123. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell*. 2017;169(2):361–371. doi:10.1016/j.cell.2017.03.035
124. Zhu P, Bu H, Tan S, et al. A novel cochlioquinone derivative, CoB1, regulates autophagy in Pseudomonas aeruginosa infection through the PAK1/Akt1/mTOR signaling pathway. *J Immunol*. 2020;205(5):1293–1305. doi:10.4049/jimmunol.1901346
125. Kayagaki N, Webster JD, Newton K. Control of cell death in health and disease. *Annu Rev Pathol*. 2024;19:157–180. doi:10.1146/annurev-pathmechdis-051022-014433
126. Wang Y, Kanneganti TD. From pyroptosis, apoptosis and necroptosis to PANoptosis: a mechanistic compendium of programmed cell death pathways. *Comput Struct Biotechnol J*. 2021;19:4641–4657. doi:10.1016/j.csbj.2021.07.038
127. Lee S, Karki R, Wang Y, Nguyen LN, Kalathur RC, Kanneganti TD. AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defence. *Nature*. 2021;597(7876):415–419. doi:10.1038/s41586-021-03875-8
128. Liu G, Pei F, Yang F, et al. Role of autophagy and apoptosis in non-small-cell lung cancer. *Int J Mol Sci*. 2017;18(2):1.
129. Mariño G, Niso-Santano M, Baehrecke EH, Kroemer G. Self-consumption: the interplay of autophagy and apoptosis. *Nat Rev Mol Cell Biol*. 2014;15(2):81–94. doi:10.1038/nrm3735
130. Lin L, Zhang L, Yu L, et al. Time-dependent changes of autophagy and apoptosis in lipopolysaccharide-induced rat acute lung injury. *Iran J Basic Med Sci*. 2016;19(6):632–637.
131. Xu Y, Kim SO, Li Y, Han J. Autophagy contributes to caspase-independent macrophage cell death. *J Biol Chem*. 2006;281(28):19179–19187. doi:10.1074/jbc.M513377200
132. Li H, Wang P, Sun Q, et al. Following cytochrome c release, autophagy is inhibited during chemotherapy-induced apoptosis by caspase 8-mediated cleavage of Beclin 1. *Cancer Res*. 2011;71(10):3625–3634. doi:10.1158/0008-5472.CAN-10-4475
133. Martyniszyn L, Szulc-Dąbrowska L, Boratyńska-Jasińska A, Struzik J, Winnicka A, Niemiałtowski M. Crosstalk between autophagy and apoptosis in RAW 264.7 macrophages infected with ectromelia orthopoxvirus. *Viral Immunol*. 2013;26(5):322–335. doi:10.1089/vim.2013.0003
134. Taabazuing CY, Okondo MC, Bachovchin DA. Pyroptosis and apoptosis pathways engage in bidirectional crosstalk in monocytes and macrophages. *Cell Chem Biol*. 2017;24(4):507–514.e504. doi:10.1016/j.chembiol.2017.03.009
135. Sagulenko V, Thygesen SJ, Sester DP, et al. AIM2 and NLRP3 inflammasomes activate both apoptotic and pyroptotic death pathways via ASC. *Cell Death Differ*. 2013;20(9):1149–1160. doi:10.1038/cdd.2013.37
136. Jounai N, Kobiyama K, Shiina M, Ogata K, Ishii KJ, Takeshita F. NLRP4 negatively regulates autophagic processes through an association with beclin1. *J Immunol*. 2011;186(3):1646–1655. doi:10.4049/jimmunol.1001654
137. Mai CT, Wu MM, Wang CL, Su ZR, Cheng YY, Zhang XJ. Palmatine attenuated dextran sulfate sodium (DSS)-induced colitis via promoting mitophagy-mediated NLRP3 inflammasome inactivation. *Mol Immunol*. 2019;105:76–85. doi:10.1016/j.molimm.2018.10.015

138. Kim MJ, Bae SH, Ryu JC, et al. SESN2/sestrin2 suppresses sepsis by inducing mitophagy and inhibiting NLRP3 activation in macrophages. *Autophagy*. 2016;12(8):1272–1291. doi:10.1080/15548627.2016.1183081
139. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134–147. doi:10.1038/nri.2017.105
140. Chen L, Zhao Y, Lai D, et al. Neutrophil extracellular traps promote macrophage pyroptosis in sepsis. *Cell Death Dis*. 2018;9(6):597. doi:10.1038/s41419-018-0538-5
141. Xie J, Zhu CL, Wan XJ, et al. GSDMD-mediated NETosis promotes the development of acute respiratory distress syndrome. *Eur J Immunol*. 2023;53(1):e2250011. doi:10.1002/eji.202250011
142. Li H, Li Y, Song C, et al. Neutrophil extracellular traps augmented alveolar macrophage pyroptosis via AIM2 inflammasome activation in LPS-induced ALI/ARDS. *J Inflamm Res*. 2021;14:4839–4858. doi:10.2147/JIR.S321513
143. Kang S, Fernandes-Alnemri T, Rogers C, et al. Caspase-8 scaffolding function and MLKL regulate NLRP3 inflammasome activation downstream of TLR3. *Nat Commun*. 2015;6:7515. doi:10.1038/ncomms8515
144. Chen H, Li Y, Wu J, et al. RIPK3 collaborates with GSDMD to drive tissue injury in lethal polymicrobial sepsis. *Cell Death Differ*. 2020;27(9):2568–2585. doi:10.1038/s41418-020-0524-1
145. Su R, Wang H, Xiao C, Tao Y, Li M, Chen Z. Venetoclax nanomedicine alleviates acute lung injury via increasing neutrophil apoptosis. *Biomater Sci*. 2021;9(13):4746–4754. doi:10.1039/D1BM00481F
146. Cao L, Mu W. Necrostatin-1 and necroptosis inhibition: pathophysiology and therapeutic implications. *Pharmacol Res*. 2021;163:105297. doi:10.1016/j.phrs.2020.105297
147. Wang X, Wu FP, Huang YR, et al. Matrine suppresses NLRP3 inflammasome activation via regulating PTPN2/JNK/SREBP2 pathway in sepsis. *Phytomedicine*. 2023;109:154574. doi:10.1016/j.phymed.2022.154574
148. Zhuang C, Chen F. Small-molecule inhibitors of necroptosis: current status and perspectives. *J Med Chem*. 2020;63(4):1490–1510. doi:10.1021/acs.jmedchem.9b01317
149. Jiang Y, Gao S, Chen Z, et al. Pyroptosis in septic lung injury: interactions with other types of cell death. *Biomed Pharmacother*. 2023;169:115914. doi:10.1016/j.biopha.2023.115914
150. Minagawa S, Yoshida M, Araya J, Hara H, Imai H, Kuwano K. Regulated necrosis in pulmonary disease. A focus on necroptosis and ferroptosis. *Am J Respir Cell Mol Biol*. 2020;62(5):554–562. doi:10.1165/rcmb.2019-0337TR
151. Gullett JM, Tweedell RE, Kanneganti TD. It's all in the PAN: crosstalk, plasticity, redundancies, switches, and interconnectedness encompassed by PANoptosis underlying the totality of cell death-associated biological effects. *Cells*. 2022;11(9). doi:10.3390/cells11091495
152. Wu C, Zhou L, Yuan H, Wu S. Interconnections among major forms of regulated cell death. *Apoptosis*. 2020;25(9–10):616–624. doi:10.1007/s10495-020-01632-2