Cell Communication and Signaling

REVIEW

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Targeting necroptosis: a promising avenue for respiratory disease treatment

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Abstract

Respiratory diseases are a growing concern in public health because of their potential to endanger the global community. Cell death contributes critically to the pathophysiology of respiratory diseases. Recent evidence indicates that necroptosis, a unique form of programmed cell death (PCD), plays a vital role in the molecular mechanisms underlying respiratory diseases, distinguishing it from apoptosis and conventional necrosis. Necroptosis is a type of inflammatory cell death governed by receptor-interacting serine/threonine protein kinase 1 (RIPK1), RIPK3, and mixed-lineage kinase domain-like protein (MLKL), resulting in the release of intracellular contents and inflammatory factors capable of initiating an inflammatory response in adjacent tissues. These necroinflammatory conditions can result in significant organ dysfunction and long-lasting tissue damage within the lungs. Despite evidence linking necroptosis to various respiratory diseases, there are currently no specific alternative treatments that target this mechanism. This review provides a comprehensive overview of the most recent advancements in understanding the significance and mechanisms of necroptosis. Specifically, this review emphasizes the intricate association between necroptosis and respiratory diseases, highlighting the potential use of necroptosis as an innovative therapeutic approach for treating these conditions.

Keywords Respiratory diseases, Necroptosis, Receptor-interacting serine/Threonine protein kinase 1 (RIPK1), RIPK3, Mixed-lineage kinase domain-like protein (MLKL)

Introduction

Respiratory diseases represent a formidable global health challenge, significantly contributing to mortality and disability rates while imposing substantial burdens on patients and caregivers alike [1]. A comprehensive international study spanning from 1990 to 2017 revealed a staggering 39.8% increase in respiratory disease cases worldwide, totaling 544.9 million individuals living with chronic respiratory conditions [2]. Alarmingly, chronic respiratory diseases emerged as the third leading cause of death in 2017, behind cardiovascular diseases and neoplasms. Hence, early detection and precise treatment strategies for these conditions are imperative.

Necroptosis, a regulated mode of cell death, intricately involves key players such as RIPK1, RIPK3 and MLKL [3]. In stark contrast to apoptosis, where dying cells

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maintain membrane integrity, necroptosis culminates in plasma membrane rupture facilitated by MLKL. This breach initiates a cascade of events leading to the release of intracellular contents, including damage-associated molecular patterns (DAMPs), inflammatory cytokines, and chemokines [4]. This intrinsic proinflammatory characteristic underscores the pivotal role of necroptosis in the pathophysiology of various diseases, including respiratory disorders. Preclinical studies using genetic knockout models and specific necroptosis inhibitors have highlighted its importance in various pathological conditions, particularly respiratory diseases [5]. These investigations emphasize the critical need to understand necroptotic pathways to devise targeted therapeutic interventions to mitigate the tissue damage and inflammation associated with respiratory diseases.

Molecular mechanisms of necroptosis

Overview of necroptosis

The history of necroptosis research is closely associated with findings on the pivotal roles played by three key proteins. Initially, the involvement of RIPK1 in regulating necrosis signalling was identified in 2000, marking a foundational milestone in the field [6]. In 2005, this pathway subsequently garnered its name "necroptosis," further solidifying its recognition [7]. The importance of RIPK3 downstream of RIPK1 was elucidated in 2009, with three independent groups concurrently implicating its kinase activity in the necroptotic cascade [8]. MLKL emerged as the terminal obligate effector in 2012, yielding a more comprehensive understanding of the pathway's mechanistic intricacies [9]. Currently, RIPK3 is the central hub in the necroptosis signalling pathway. Upon receiving upstream signals, RIPK3 undergoes polymerization into amyloid fibrils via an RIP homotypic interaction motif (RHIM) [10]. This molecular event is pivotal, as it sets the stage for the formation of a large heteromeric complex termed the necrosome, where RIPK1 and RIPK3 converge. Within this complex, RIPK3 catalyses the phosphorylation of its downstream effector MLKL, activating it for its crucial role in necroptosis execution. Despite significant advancements, the precise mechanism underlying MLKL-mediated membrane rupture remains incompletely understood. Nevertheless, extensive structural characterization has provided insights into the architecture of MLKL. Compared with an N-terminal four-helix bundle domain and a C-terminal pseudokinase domain bridged by a two-helix linker termed the brace region, MLKL has a sophisticated modular structure [11]. Notably, the four-helix bundle domain is responsible for membrane interaction and permeabilization, endowing MLKL with its potent lytic executioner function. These structural insights not only enhance our understanding of the necroptotic machinery but also present promising avenues for targeted therapeutic interventions aimed at modulating necroptotic cell death in various pathological contexts.

Regulation of necroptotic signalling

Classical necroptotic pathway

Necroptosis, a pivotal form of regulated cell death, hinges predominantly on the activation of death receptors such as tumour necrosis factor receptor (TNFR), Fas/CD95, and TRAIL receptors [12, 13] (Fig. 1). Among these pathways, the classical necroptotic pathway initiated by TNF-α has been extensively characterized. Upon TNF-α binding to TNFR1, a crucial membrane signalling complex termed "complex I" is formed, orchestrating the fate of the cell. Complex I is comprised of a myriad of components, including TNFR1-associated death domain protein (TRADD), Fas-associated death domain protein (FADD), RIPK1, members of the tumour necrosis factor receptor-associated factor (TRAF) family of proteins, and cellular inhibitor of apoptosis proteins (cIAPs) 1/2. TRADD serves as a crucial adaptor molecule, facilitating the recruitment of RIPK1 to TNFR1, thereby initiating downstream signalling events [14–16]. Upon activation, cIAP1/2 and TRAF2/5 orchestrate the ubiquitination of RIPK1, thereby stabilizing complex I. Importantly, this stabilization serves as a pivotal checkpoint, dictating whether the cell progresses towards prosurvival or death pathways [17–19]. Notably, in circumstances favourable for cell survival, an alternative pathway is initiated, culminating in the activation of nuclear factor kappa B (NF-κB) [20] and mitogen-activated protein kinase (MAPK) signalling cascades [21]. NF-κB signalling plays a paramount role in counteracting the cytotoxic effects of TNF-α, with its prosurvival effects mediated by cIAP1/2 and cellular FLICE-like inhibitory protein [22]. Collectively, these intricate signalling events underscore the dynamic interplay between prosurvival and prodeath pathways in the context of necroptosis, shedding light on the multifaceted regulatory mechanisms orchestrating cellular fate in response to death receptor activation.

The delicate balance between the prosurvival and cell death pathways in necroptosis depends on the ubiquitination status of RIPK1 [23]. This pivotal protein serves as a fulcrum, orchestrating the fate of the cell in response to death receptor activation. Notably, the removal of the ubiquitin chain from RIPK1, facilitated by cylindromatosis (CYLD)-mediated deubiquitylation, marks a critical turning point [24]. This deubiquitylation event destabilizes complex I, prompting RIPK1 dissociation and subsequent interaction with FADD through its death domain. The recruitment of pro-caspase 8 to this newly formed complex, termed complex IIa, ensues, thereby initiating

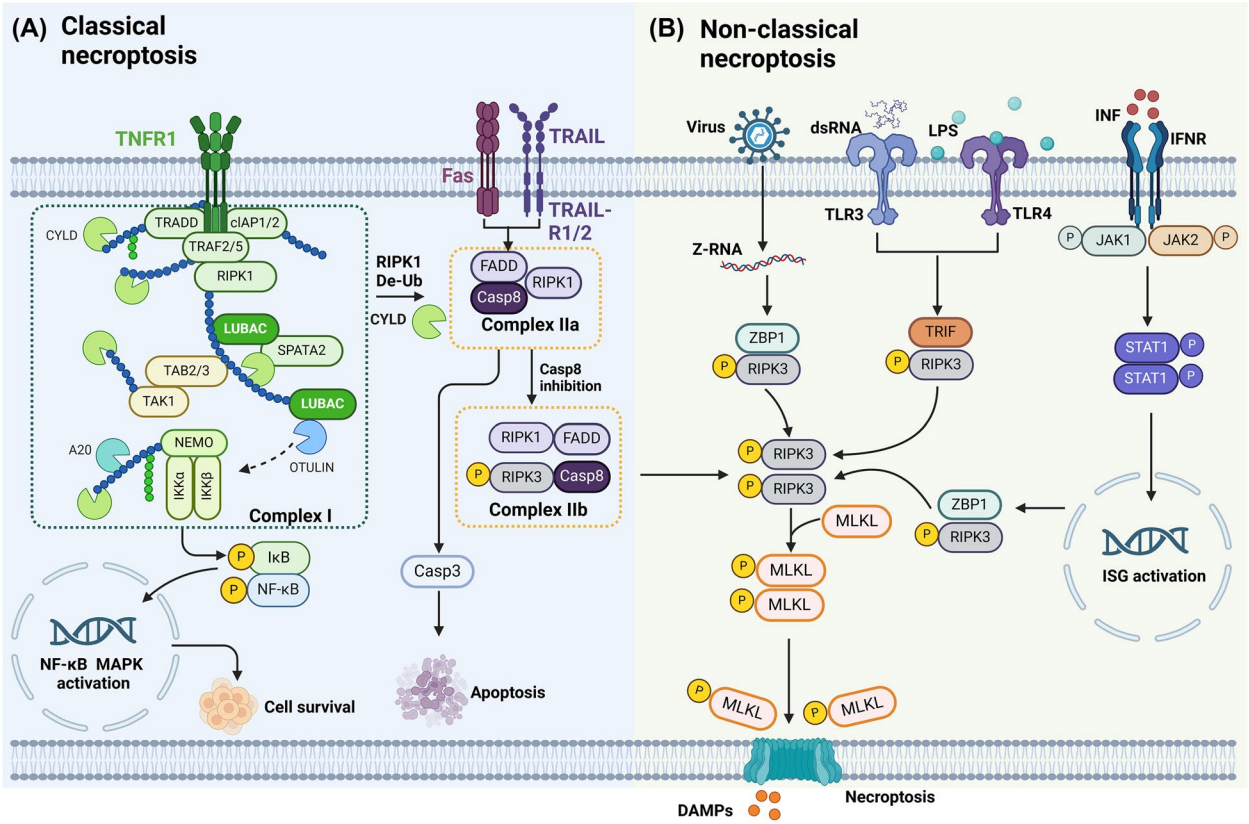

Fig. 1 Regulation of necroptotic signalling. **A** Classical necroptotic pathways. Necroptosis begins with the activation of death receptors such as necrosis factor receptor (TNFR) 1, Fas, and TRAIL receptors, leading to the assembly of "complex I" on the cell membrane. This complex includes TRADD, RIP1, TRAF2/5, and cIAP1/2, acting as a crucial decision point between cell survival and death pathways. TRADD recruits RIP1 to TNFR1, while cIAP1/2 and TRAF2/5 promote RIP1 ubiquitination, stabilizing complex I and activating pathways like NF-κB and MAPK for cell survival. Upon RIP1 deubiquitination, complex IIa forms, involving FADD, TRADD, RIP3, and caspase 8, suppressing apoptosis under normal conditions. However, if caspase-8 is inactive, RIPK1-RIPK3 interaction leads to complex IIb formation, initiating MLKL phosphorylation and oligomerization, triggering necroptosis. **B** Non-classical necroptotic signaling. Toll-like receptor (TLR)3 and TLR4, activated by dsRNA and LPS respectively, trigger necroptosis directly through RHIM domain-mediated TRIF and RIPK3 association. Viral nucleic acids activate RHIM-containing ZBP1, inducing RIP3-MLKL-dependent necroptosis, independently of RIPK1. Interferon (IFN)-driven necroptosis involves JAK/STAT-dependent transcription. These pathways converge on MLKL activation, the necroptosis executor

the apoptotic cascade [25]. However, in scenarios where caspase-8 is either inactivated or inhibited, an alternative pathway is activated. Under such conditions, RIPK1 undergoes autophosphorylation at serine 166, promoting its interaction with RIPK3 via their RHIM domains [26, 27]. This association, known as an RIP homotypic interaction, culminates in the assembly of the necrosome, or complex IIb, which activates downstream effector molecules [28]. Within the necrosome, phosphorylation and subsequent oligomerization of MLKL occur, positioning MLKL as the ultimate executioner of necroptosis [29]. This orchestrated sequence of events highlights the dynamic interplay between apoptotic and necroptotic pathways, underscoring the intricacies of cellular fate determination in response to death receptor signalling. Such insights not only deepen our understanding of the necroptotic machinery but also reveal potential therapeutic targets for modulating cell death pathways in various pathological contexts.

Noncanonical necroptotic pathway

Necroptosis, a dynamic form of PCD, can be initiated by a diverse array of stimuli that act through multiple receptors and intracellular sensors, in addition to classical death receptors (Fig. 1). These stimuli trigger intricate signalling cascades that ultimately converge on the activation of MLKL, the principal executor of necroptosis. Notably, toll-like receptors (TLRs), such as TLR3 and TLR4, play crucial roles in directly inducing necroptosis upon activation by specific ligands such as double-stranded (ds) RNA and lipopolysaccharide (LPS), respectively [30, 31]. TLR3- and TLR4-mediated

necroptosis hinges on the recruitment of RIPK3 through an RHIM domain-dependent association with TRIF, revealing diverse pathways leading to necroptotic cell death. Furthermore, the RHIM domain-containing protein Z-DNA binding protein 1 (ZBP1), also known as DAI or DLM-1, has emerged as a key mediator of necroptosis triggered by viral nucleic acids [32–34]. Importantly, ZBP1 mediates necroptosis independently of RIPK1, further highlighting the complexity of necroptotic signalling pathways.

Interferons (IFNs) also play pivotal roles in driving necroptosis through distinct mechanisms. IFN-driven necroptosis can be facilitated by Janus kinase 1 (JAK1) and signal transducer and activator of transcription 1 (STAT1)-dependent transcription, leading to the formation of a RIPK1-RIPK3 complex [35, 36]. These findings underscore the intricate interplay between various receptors and sensors in orchestrating necroptotic cell death through different pathways. While death receptors, TLRs, and IFN receptors each contribute to necroptosis induction, the underlying mechanisms involve distinct interactions between RHIM domain-containing proteins such as RIPK1, RIPK3, TRIF, and ZBP1. Despite this diversity, all pathways ultimately converge on the activation of MLKL, underscoring its central role as the effector molecule in necroptosis execution. Such insights not only deepen our understanding of necroptotic signalling but also offer promising avenues for therapeutic interventions targeting necroptosis in various pathological contexts.

Posttranslational modifications of key players in necroptosis

Posttranslational modifications (PTMs) are essential biochemical alterations that occur after protein synthesis and influence protein structure, function, and localization. In the context of necroptosis, PTMs serve as critical regulators, modulating the activity and function of key molecules involved in this PCD pathway. For example, the phosphorylation of RIPK1 and RIPK3 can either promote or inhibit necroptosis, depending on the specific residues targeted [37]. Additionally, the ubiquitination of RIPK1 can direct its localization and interactions within the necrosome complex, thereby influencing downstream signalling events [37]. Thus, understanding the diverse landscape of PTMs in necroptosis may reveal potential therapeutic targets for manipulating this cell death pathway in various disease contexts.

Phosphorylation

Autophosphorylation at S166 represents a crucial event in RIPK1 activation, driving kinase-dependent cell death and inflammatory responses [38]. However, the prodeath function of RIPK1 can be modulated and restrained by various kinases. For example, TAK1 and MAPKAPK2 (MK2) play key roles in limiting RIPK1-mediated cell death by phosphorylating specific residues, such as S320 (human), S321 (mouse) and S336 (mouse) [39, 40]. In addition to its direct effect on RIPK1, TAK1 activates IKKα/β, which further suppresses RIPK1-induced cell death by phosphorylating S25 (in humans and mice) [41]. ULK1 achieves this by phosphorylating RIPK1 at S357 (human), thus impeding the assembly of the necrosome and subsequent necroptosis [42]. The autophosphorylation sites T231/S232 (in murine RIPK3) [43] and S227 (in human RIPK3) play pivotal roles in regulating RIPK3 activity and subsequent necroptotic signalling pathways [44]. These phosphorylation events are intricately orchestrated by various cellular kinases and phosphatases. Members of the casein kinase 1 (CK1) family, including CK1δ and CK1ε, have been identified as direct regulators of RIPK3 phosphorylation at these sites [44]. Furthermore, the dephosphorylation of RIPK3 by protein phosphatase 1B (PPM1B) provides another layer of regulation in necroptotic signalling [45]. PPM1B acts as a negative regulator by counteracting the phosphorylation-mediated activation of RIPK3, thereby attenuating necroptosis. RIPK3 plays a central role in orchestrating the phosphorylation of MLKL at critical sites, including S345 (in murine MLKL) [46] and T357/S358 (in human MLKL) [47]. This phosphorylation event induces structural alterations in MLKL, triggering its oligomerization, a pivotal step in executing necroptosis. However, emerging evidence suggests a nuanced regulatory network governing MLKL phosphorylation and function. For example, under conditions of serum and amino acid deprivation, an alternative pathway involving calcium/calmodulin-dependent protein kinase II (CAMK2/CaMKII) has emerged as a key regulator of MLKL phosphorylation at the same sites, promoting autophagy rather than necroptosis [48]. This divergence underscores the versatility of MLKL as a signalling node responsive to distinct cellular cues.

Ubiquitination

Ubiquitination, a posttranslational modification, intricately regulates signalling pathways that orchestrate cell fate decisions, including the pivotal process of necroptosis [49, 50]. Among the myriad players in this intricate dance, RIPK1 is central and is subject to a complex web of ubiquitin-mediated modifications. Notably, RIPK1 can undergo ubiquitination at various lysine residues, each of which has distinct functional consequences [51]. Pellino 1 (PELI1), an E3 ubiquitin ligase, orchestrates K63-linked ubiquitylation at K115 on RIPK1, which is crucial for the assembly of death-inducing complexes [52]. LUBAC, another E3 ubiquitin ligase,

regulates RIPK1 linear ubiquitylation, curbing its activity and restraining necroptosis. Conversely, disruption of LUBAC amplifies RIPK1 activity and necroptotic signalling, underscoring the delicate balance maintained by M1-linked ubiquitylation [53–55]. A20, a potent NF-κB signalling inhibitor, further intricately modulates RIPK1 ubiquitination, stabilizing the ubiquitin scaffold on complex I to mitigate TNF-α cytotoxicity [56, 57]. Moreover, E3 ubiquitin ligases such as Mind bomb-2 (MIB2) and the carboxy terminus of Hsp70-interacting protein (CHIP) have emerged as critical checkpoints in negating necroptosis through their targeted ubiquitination of RIPK1 at specific lysine residues [58, 59]. However, a comprehensive understanding of their precise roles requires further experimental investigation. Intriguingly, the reversible nature of RIPK1 ubiquitination is governed by deubiquitinating enzymes (DUBs), such as CYLD and OTULIN, which hydrolyse ubiquitin chains, fostering the assembly of complex IIb and potentiating necroptosis [60, 61]. The intricate regulation of RIPK3 involves posttranslational modifications mediated by several E3 ubiquitin ligases. PELI1 has been identified as a key player that targets K363 of RIPK3 for K48-linked ubiquitylation, marking it for proteasomal degradation [62]. Similarly, through targeting K55 and K363 of RIPK3, the carboxyl terminus of Hsc70-interacting protein (CHIP) facilitates its degradation via the proteasome machinery [63]. Moreover, Parkin, known for its role in mitophagy, has been implicated in the ubiquitylation of RIPK3 at the K197, K302, and K364 residues, leading to its proteasomal turnover [64]. Another E3 ligase, TRIM25, targets K501 of RIPK3 for ubiquitination, further contributing to its degradation [65]. In contrast, ubiquitin-specific peptidase 22 (USP22) acts as a positive regulator of necroptosis by removing ubiquitin chains from RIP3 at the K42, K351, and K518 residues, thereby promoting necrosome assembly and subsequent necroptotic signalling [66]. Like RIPK1 and RIPK3, endogenous MLKL undergoes ubiquitylation at specific lysine residues, including K51, K77, K172, and K219 [67]. Among these sites, K219 has been identified as crucial for MLKL-mediated membrane disruption and necroptosis, highlighting the importance of ubiquitylation in regulating MLKL function [68]. Furthermore, another investigation revealed additional ubiquitylation sites within the four-helix bundle (4HB) domain of MLKL, including K9, K51, K69, and K77 [69, 70]. Intriguingly, a MLKL-USP21 fusion protein, a deubiquitylating enzyme capable of removing all ubiquitin moieties from MLKL in vitro, was shown to induce cell death independently of RIPK3 in Mlkl-deficient cells [71]. These findings suggest a critical role for MLKL ubiquitylation in limiting basal levels of activated MLKL to prevent spontaneous cell death.

SUMOylation

SUMOylation, a posttranslational modification involving the attachment of small ubiquitin-like modifier (SUMO) proteins to target proteins, has emerged as a pivotal regulator of diverse cellular processes, including necroptosis mediated by RIPK1 [72]. The intricate interplay between SUMOylation and RIPK1 functionality adds another layer of complexity to the regulation of cell fate decisions. Research suggests that RIPK1 can undergo SUMOylation at specific lysine residues, thereby modulating its activity and downstream signalling [72]. For example, studies have implicated the SUMOylation of RIPK1 at lysine 45 (K45) as a critical event in preventing its death-promoting functions. SUMOylation at K45 impedes RIPK1 kinase activity and its recruitment to necrosomes, thus inhibiting necroptosis initiation [73]. Furthermore, SUMOylation of RIPK1 has been proposed to influence its interaction with other regulatory proteins. For example, SUMOylation at specific sites may promote the association of RIPK1 with SUMO-interacting motifs (SIMs) present on various proteins, thereby modulating downstream signalling pathways. Additionally, SUMOylation of RIPK1 might regulate its ubiquitination status, leading to alterations in its stability or subcellular localization, further impacting necroptosis regulation. Moreover, emerging evidence suggests that there is crosstalk between SUMOylation and other posttranslational modifications of RIPK1, such as ubiquitination [74].

O-GlcNAcylation

O-GlcNAcylation is a dynamic PTM involving the attachment of a single N-acetylglucosamine (GlcNAc) moiety to serine or threonine residues of nuclear and cytoplasmic proteins [75]. O-GlcNAc transferase (OGT)-mediated O-GlcNAcylation of RIPK3 at T467 prevents the RIPK1/3 heterointeraction and the RIPK3/3 homointeraction, thus dampening inflammation and necroptosis [76]. Park et al. [77] reported that O-GlcNAcylation of RIPK3 hinders its phosphorylation and binding to RIPK1. Increased O-GlcNAcylation has been demonstrated to alleviate AD pathology by reducing the Aβ burden, preventing neuronal loss, mitigating neuroinflammation, preserving mitochondrial function, and restoring the M2 phenotype and phagocytic activity of microglia. Seo et al. [78] reported that O-GlcNAcylation of RIPK1 at serine 331 in humans (corresponding to serine 332 in mice) inhibits the phosphorylation of RIPK1 at serine 166, which is necessary for the necroptotic activity of RIPK1.

Necroptosis in respiratory diseases

Chronic lung diseases

Necroptosis can result in circulatory failure, organ injury, and lethal lung tissue injury. While the causes and

outcomes of these injuries differ substantially, necroptosis is often observed in both airway epithelial and endothelial injuries. In the following sections, we explore the existing experimental and clinical evidence that supports the involvement of necroptosis in chronic lung diseases (Fig. 2).

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation due to chronic inflammation, has been extensively researched in recent years [79]. Eeckhoutte et al. [80] notably reported an increase in RIPK1 expression across various cell types in COPD patients, including airway epithelial cells, type I alveolar epithelial (ATI) cells and ATII cells. Similarly, Lu et al. [81] reported elevated levels of p-RIPK3 and p-MLKL proteins in the lung tissue of patients with severe COPD, alongside increased total MLKL protein levels in macrophages. Long-term smoking is a primary aetiological factor in COPD pathogenesis. In a cigarette smoke (CS)-induced COPD mouse model, increased ATI cell necroptosis was evident. Pharmacological inhibition of RIPK1 or RIPK3 activity, genetic knockout of *Ripk1* or *Ripk3* in murine models, or deletion of MLKL significantly alleviated ATI necroptosis, thereby ameliorating CS-induced airway inflammation and remodelling and

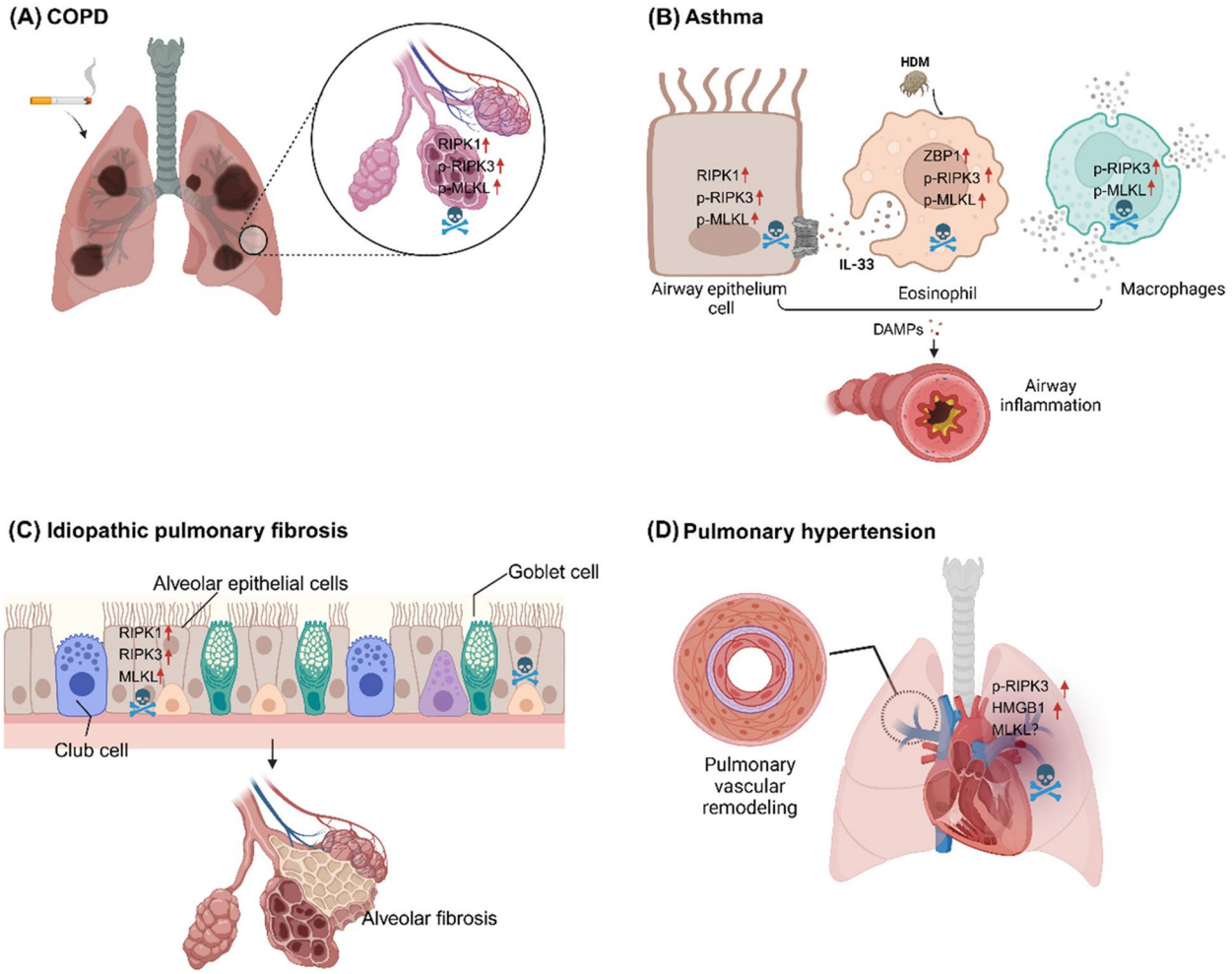

Fig. 2 Necroptosis in chronic lung diseases. **A** Cigarette smoke induces necroptosis in alveolar epithelial cells in individuals with COPD. This process releases damage-associated molecular patterns (DAMPs), exacerbating inflammation and tissue damage, thereby contributing to disease progression. **B** Necroptosis in airway epithelial cells, neutrophils, and macrophages contributes to airway inflammation and hyperresponsiveness, thereby promoting the development of asthma. **C** In idiopathic pulmonary fibrosis, alveolar epithelial cells also undergo necroptosis, releasing DAMPs. This process induces an inflammatory response, promoting the progression of pulmonary fibrosis. **D** In pulmonary hypertension, necroptosis and subsequent HMGB1 release are reported to result in pulmonary vascular remodeling, although the role of mixed-lineage kinase domain-like protein (MLKL) in this process has not been conclusively determined

ultimately preventing emphysema. These findings underscore the pivotal role of necroptosis in COPD pathogenesis. In another study [82], CS extract-induced necroptosis of alveolar epithelial cells was associated with increased release of DAMPs, increasing the expression of the pro-inflammatory cytokines TNF-α and interleukin (IL)-6, thereby exacerbating the inflammatory cascade and hastening alveolar epithelial cell death. Notably, pharmacological inhibition of RIPK3 by GSK-872 effectively mitigated the lung inflammation and emphysema induced by CS in murine models. Additionally, Faiz et al. [83] established an association between the CFLAR gene, encoding the cellular death regulatory protein cellular-FLICE inhibitory protein (c-FLIP), and the release of DAMPs induced by CS. Comparatively, bronchial biopsies from smokers presented changes in the relative levels of c-FLIPS and c-FLIPL transcripts, which was consistent with alterations in necroptosis. In vitro experiments revealed that CS exposure significantly reduced CFLAR expression in bronchial epithelial cells, exacerbating vulnerability to necroptosis and subsequent release of DAMPs [83]. Furthermore, Wang et al. [84] identified dysregulated necroptosis-related genes (NRGs) in COPD, demonstrating associations with inflammation and the immune response.

Mounting evidence indicates that necroptosis significantly contributes to COPD pathogenesis through its interaction with various regulatory cell death pathways. Mizumura et al. [85] demonstrated that cigarette smoke induces mitochondrial dysfunction and necroptosis in alveolar epithelial cells and bronchial epithelial cells by promoting the expression of the mitochondrial autophagy regulator PTEN-induced kinase 1 (PINK1). Administration of the autophagy inhibitor Mdivi-1 or knockout of the Pink1 gene significantly attenuated cigarette smoke-induced pulmonary inflammation and emphysema in murine models [85]. These findings underscore the potential therapeutic importance of targeting the mitochondrial autophagy-dependent necroptotic pathway for COPD treatment. Additionally, the potential roles of oxidative stress and iron metabolism disorders in regulating necroptosis and ferroptosis in COPD have been reviewed [86], which suggests that exploring the interplay among autophagy, necroptosis, and ferroptosis in COPD holds promise for future research.

Asthma

The role of necroptosis in asthma pathogenesis has gained substantial attention and research focus in recent years. Oikonomou et al. [87] reported that necroptosis of airway epithelial cells (AECs) exacerbates allergic airway inflammation. Compared with wild-type mice, *Ripk1*$^{-/-}$ mice exhibited a notable reduction in airway inflammation in an OVA-induced asthma model. *Mucin 1* (MUC1), a highly glycosylated transmembrane mucin, is abundantly expressed on the surface of respiratory epithelial cells and exerts both anti-inflammatory and antiapoptotic effects [88]. TNF-α induces necroptosis in human AECs and enhances MUC1 expression, although the precise mechanism requires further elucidation [89]. Zhang et al. [90] reported that downregulation of MUC1 induced glucocorticoid resistance in asthmatic mice by augmenting TNF-α-induced necroptosis in human AECs. Cerps et al. [91] reported that asthma exacerbation induced by house dust mites (HDMs) in a mouse model with antiviral interferon-β (IFN-β) deficiency led to increased protein expression of RIPK3 and p-MLKL in mouse bronchoalveolar lavage fluid, suggesting a potential mechanism for IFN-β deficiency-induced asthma exacerbation. Necroptosis serves as a direct mechanism for IL-33 release and the initiation of a type 2 immune response. Shlomovitz et al. [92] used the human and murine necroptosis mutation inhibitor GW806742X in an Aspergillus extract-induced asthma model, which effectively blocked eosinophil necroptosis and IL-33 release. In an HDM-induced asthma mouse model and in macrophages, Du et al. [93] demonstrated that the inhibition of polymerase 1 and transcript release factor (PTRF) reduced the expression of IL-33, ZBP1, p-RIPK3, and p-MLKL, among others. IL-33 deletion also reduced the expression of ZBP1, p-RIPK3, and p-MLKL in asthmatic mice, suggesting a potential regulatory role of IL-33 in the necroptotic pathway [93]. He et al. [94] recently demonstrated the activation of the necroptosis signalling pathway in asthma patients and animal models, highlighting the heightened sensitivity of eosinophils to necroptosis, characterized by significantly higher levels of p-MLKL than that in neutrophils. Eosinophil granules released from ruptured eosinophils may induce airway inflammation. Radonjic et al. [95] demonstrated that eosinophil lysis is associated with the activation of RIPK3/MLKL and that pharmacological inhibition of RIPK3 significantly reduces airway inflammation in asthmatic mice. These findings collectively illuminate the intricate role of necroptosis in asthma pathogenesis and present promising avenues for targeted therapeutic interventions.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal chronic interstitial lung disease characterized by alveolar epithelial cell injury, diminished repair capacity, and deposition of the extracellular matrix, all of which stem from the sustained activation of fibroblasts and myofibroblasts [96]. Necroptosis of ACEs contributes significantly to the pathophysiology of IPF. Lee et al. [97] reported a significant increase in RIPK3 protein

expression in the lung tissues of IPF patients, confirming necroptosis in primary AECs. Subsequent in vivo studies demonstrated that *Ripk3*$^{AEC-/-}$ IPF mice exhibited reduced lung fibrosis and inflammation compared with bleomycin-induced wild-type IPF mice, along with decreased levels of high mobility group protein 1 (HMGB1) and IL-1β in lung tissue [96]. Genetic factors, including mutations in the surfactant protein A1 (SFTPA1) gene, are also implicated in the aetiology of IPF [98]. Takezaki et al. [99] demonstrated that SFTPA1 mutation promotes necroptosis in ATII cells through c-Jun N-terminal kinase (JNK)-mediated activation of RIPK3, contributing to IPF development. This study underscores the therapeutic potential of targeting the necroptotic pathway in hereditary IPF. Tao et al. [100] reported that necrostatin-1 (Nec-1), an RIPK1 inhibitor, significantly attenuated lung inflammation and fibrosis in a silica-induced silicosis mouse model. Additionally, necroptosis-associated differentially expressed genes, including MLKL, are upregulated in fibrotic lung tissues, particularly ATII cells, which are correlated with proinflammatory immune cell infiltration [101]. Therefore, necroptosis in ATII cells may contribute to IPF pathogenesis by activating the immune response, necessitating further exploration.

Pulmonary hypertension

Pulmonary hypertension (PH) is a progressive and frequently fatal pulmonary vascular disease characterized by right heart failure and high mortality rates [102]. Zemskova et al. [103] noted markedly higher serum HMGB1 levels in male PH patients than in female patients. Subsequent studies revealed that necroptosis in human pulmonary artery endothelial cells and smooth muscle cells led to HMGB1 release, activating TLR4 and increasing the number of circulating HMGB1 dimers [103]. This mechanism contributes to elevated right ventricular systolic pressure in a rat model of chronic hypoxia combined with Sugen 5416-induced pulmonary arterial hypertension in males compared with females, explaining the sex susceptibility observed in clinical settings. Furthermore, lung tissue and plasma levels of RIPK3 were significantly elevated and positively correlated with the extent of right ventricular hypertrophy in a model of pulmonary arterial hypertension induced by wild lily alkaloids [104]. Xiao et al. [105] reported that RIPK3-mediated necroptosis activates the TLR2 and NLRP3 inflammatory signalling pathways, exacerbating inflammation and immune responses and inducing pulmonary vascular remodelling in rats with pulmonary arterial hypertension induced by monocrotaline. These findings underscore the involvement of necroptosis-induced inflammation in pulmonary vascular remodelling, which contributes to the progression of PH. Jarabicová et al. [104] reported a marked increase in plasma RIPK3 levels in a monocrotaline-induced rat model of PH, which was positively correlated with right ventricular hypertrophy. These findings suggest that the upregulation of the pThr231/Ser232-RIPK3 pathway induces necroptosis and pyroptosis, thereby contributing to PH pathology.

Necroptosis in lung cancer

In clinical settings, the resistance of lung cancer cells to death, immune evasion, and chemotherapy significantly impacts treatment efficacy. Recently, necroptosis has gained considerable attention for its role in responsiveness to lung cancer treatment. Notably, the mRNA expression levels of RIPK1, RIPK3, and MLKL are lower in tumour tissues from squamous cell carcinoma and lung adenocarcinoma (LUAD) patients than in normal tissues [106]. Additionally, LUAD necroptosis-related genes (NRGs) are closely correlated with patient survival, patient prognosis, and tumour immune prediction [107, 108]. RIPK3 plays a dual role in lung cancer progression. High RIPK3 expression in early-stage non-small cell lung cancer (NSCLC) patients is correlated with improved local control and progression-free survival [109]. Wang et al. demonstrated that ablative hypofractionated radiation therapy (HFRT) preferentially induces necroptosis in NSCLC cells with high RIPK3 expression, promoting HMGB1 release [109]. RIPK3 expression renders lung cancer cells sensitive to the cytotoxic effects of anticancer drugs such as cisplatin, etoposide, vinorelbine, and doxorubicin, whereas low RIPK3 expression is correlated with poor chemotherapy response in NSCLC patients [110]. Methylation of the RIPK3 promoter suppresses the necroptotic pathway in lung cancer cells, while demethylation partially restores RIPK3 expression and increases chemotherapy-induced cell necroptosis, thereby enhancing the chemotherapy response [110].

Regulating necroptosis is a crucial mechanism of action for many lung cancer therapeutic agents. ID1, an oncogenic factor, enhances the sensitivity of NSCLC cells to gefitinib by activating the RIPK3/MLKL-dependent necroptotic pathway when it is overexpressed [111]. Cisplatin induces necroptosis in lung cancer A549 cells by activating the MLKL-PITPα signalling pathway [112]. Moreover, apurinic/apyrimidinic endonuclease 1 (APE1) is highly expressed in lung cancer patients and is correlated with poor prognosis. The APE1 inhibitor NO.0449 – 0145 inhibits tumour growth and enhances the sensitivity of NSCLC cells to cisplatin and erlotinib by inducing necroptosis in A549 and NCI-H460 lung cancer cells [113]. Diao et al. [114] treated lung adenocarcinoma cells expressing p-Casp8 with paclitaxel and reported that p-Casp8 promotes necroptosis initiation

and the interaction between RIPK1/RIPK3, further evaluating the efficacy of paclitaxel in treating lung adenocarcinoma. Immune checkpoint inhibitor resistance is a major challenge in lung cancer treatment, and extracellular vesicles in the tumour microenvironment are associated with chemotherapy-related immune suppression and metastasis. Petanidis et al. [115] induced RIPK3/TNF-α-dependent necroptosis in metastatic lung cancer patient cells through combined carboplatin treatment with exosomal Kras intervention, accompanied by differential expression of immune-suppressive miR-146/miR-210 regulatory factors. Other antitumour drugs, such as shikonin [116] and 2-methoxy-6-acetyl-7-methyljuglone [117], have been shown to exert antitumour activity by inducing necroptosis in lung cancer cells.

Mutations in necroptosis-related genes have emerged as a novel therapeutic approach for targeting cancer cells. HS-173, a drug capable of inducing RIPK3-mediated necroptosis, reduces the viability of lung cancer cells expressing RIPK3 in a dose-dependent manner [118]. In a xenograft lung cancer mouse model, HS-173 inhibited tumour growth by promoting necroptosis [118]. The E3 ligase Skp2 is frequently overexpressed in human NSCLC tissues and cell lines, leading to MLKL ubiquitination and degradation. Inhibiting skp2 partially restores MLKL levels and sensitizes NSCLC cells to cisplatin both in vitro and in vivo [119]. Thus, strategies targeting Skp2-mediated MLKL degradation may overcome chemotherapy resistance in NSCLC patients. Mutations in the tumour suppressor gene p53 are prevalent in 75–90% of small cell lung cancers. Tang et al. [120] reported that high-level expression of mutant p53 in lung cancer tissues is associated with decreased expression of the deacetylase sirtuin 3 (SIRT3). SIRT3 regulates mutant p53 stability by controlling its ubiquitination and inhibits the growth of human small cell lung cancer cells by promoting apoptosis and necroptosis [120]. C/EBP homologous protein (CHOP) is a transcription factor involved in endoplasmic reticulum stress-induced apoptosis. LGH00168, a CHOP activator, significantly suppressed tumour growth in A549 xenograft mice. Although LGH00168 treatment does not induce apoptosis in A549 cells, it triggers mitotic ROS production, leading to RIPK1-dependent necroptosis characterized by cell swelling, plasma membrane rupture, lysosomal membrane permeabilization, MMP collapse, and Casp8 inhibition [121]. Metastasis remains a leading cause of mortality in cancer patients. Bolik et al. [122] identified the membrane-bound metalloproteinase ADAM17 on endothelial cells as a key driver of metastasis. ADAM17-mediated shedding of the TNFR1 ectodomain and subsequent γ-secretase complex processing are essential for TNF-induced necroptosis [122]. Knockdown or short-term drug inhibition of ADAM17 expression in endothelial cells prevents the formation of long-term metastatic lung tumours, indicating that ADAM17 is a promising new target for antimetastatic and late-stage cancer therapy.

Additionally, necroptosis is implicated in the sensitivity of lung cancer cells to immunotherapy. Workenhe et al. [123] reported that the inflammatory milieu resulting from necroptotic pathway activation can increase the responsiveness of lung cancer cells to immune checkpoint inhibitors. Paradoxically, increased RIPK3 expression is correlated with an unfavourable prognosis in NSCLC patients [124]. Furthermore, the level of necroptosis inversely correlates with the expression of immune checkpoint proteins in lung cancer patient tumour tissues, indicating enhanced efficacy of immune checkpoint inhibitors when combined with the immunosuppressant FTY720, leading to improved clinical outcomes [125] Saddoughi et al. [126] demonstrated that the sphingosine analogue FTY720 targets I2PP2A/SET, inhibiting lung tumour growth through RIPK1 kinase domain-mediated activation of protein phosphatase 2 A (PP2A) and necroptosis. However, some studies suggest that necroptosis of tumour cells induces tumour necrosis and facilitates tumour metastasis [127]. Patel et al. [128] reported that RIPK1 inhibitors can alleviate inflammatory diseases but do not impede tumour growth or metastasis, suggesting a dual role for necroptosis in lung cancer.

Necroptosis in acute lung injury

Acute lung injury (ALI) is a severe condition characterized by sudden exacerbations and extensive lung inflammation and is commonly initiated by factors such as infection, trauma, and systemic inflammation [129]. The following discussion explores the existing experimental and clinical evidence concerning the role of necroptosis in the typical triggers of human ALI (Fig. 3). Previous studies have shown increased levels of HMGB1 in both the plasma and bronchial lavage fluid of ALI patients and in animal models of ALI induced by LPS [130]. Neutralizing HMGB1 with antibodies ameliorated LPS-induced ALI [130], suggesting a likely link between necroptosis and the development of ALI. Chen et al. [131] reported the induction of LPS-induced necroptosis and activation of NOD-like receptor protein 3 (NLRP3) in the lung cells of ALI mice. The RIPK3 inhibitor GSK-872 notably inhibited necroptosis and NLRP3 activation, leading to decreased production of IL-1β and IL-18, reduced inflammatory cell infiltration, and improvements in LPS-induced lung tissue injury. Furthermore, recent research by Li et al. [132] revealed the interplay between the NLRP3 signalling pathway and necroptosis, showing that *Pseudomonas aeruginosa* (PA) induces changes in the mitochondrial membrane potential via MLKL-dependent

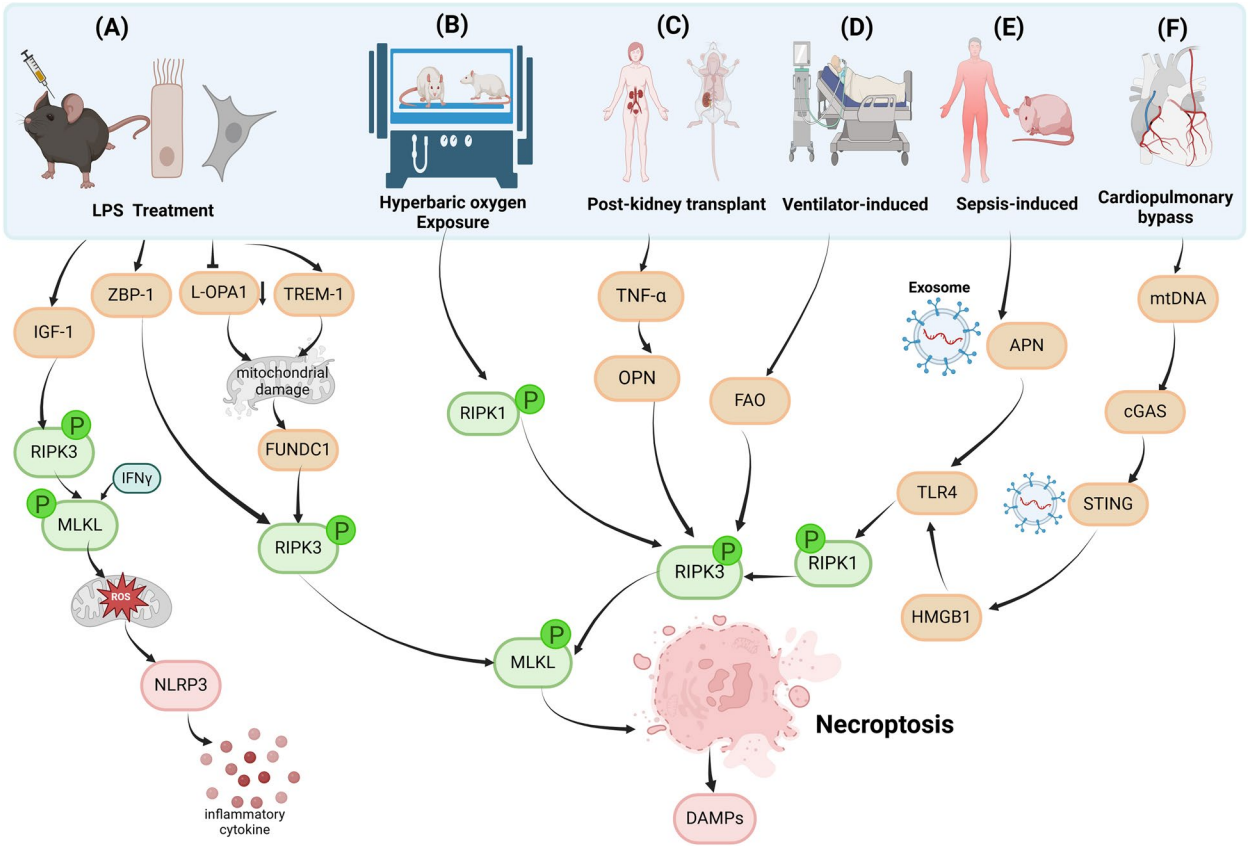

Fig. 3 Necroptosis plays a significant role in acute lung injury (ALI). **A** Lipopolysaccharide (LPS) exhibits dual effects: it activates RIPK3, triggering necroptosis via IGF and ZBP1, while also inducing mitochondrial damage through L-OPA and TREM-1, leading to upregulated FUNDC1 expression and further activation of RIPK3. **B** Hyperbaric oxygen exposure directly initiates the RIPK1-RIPK3-MLKL pathway, culminating in necroptosis. **C** Kidney transplantation may cause pulmonary ischemia-reperfusion injury, elevating TNF-α and OPN release, thereby promoting necroptosis and worsening lung damage. **D** Ventilator-induced ALI (VILI) is linked to impaired FAO function, with FAO-dependent RIPK3-mediated necroptosis being a key pathogenic mechanism. **E** Sepsis-induced ALI results in elevated exosomal APN expression, inducing necroptosis in alveolar epithelial cells. **F** Cardiopulmonary bypass (CPB) exacerbates ALI by facilitating exosomal release of HMGB1 via the mtDNA/cGAS/STING pathway, promoting necroptosis

necroptosis signalling, leading to ROS release and NLRP3 activation, thereby causing ALI. Moreover, ALI is linked to a cytokine storm, in which multiple proinflammatory cytokines modulate necroptosis. Hao et al. [133] reported that even at low concentrations (1 ng/mL), IFNγ preferentially activated necroptosis in lung epithelial cells, suggesting its potent role as an enhancer of necroptosis in these cells.

In ALI, mitochondrial function closely correlates with necroptosis in alveolar epithelial cells. Long optic atrophy protein 1 (L-OPA1) serves as a crucial mitochondrial inner membrane fusion protein, and its deficiency compromises mitochondrial function. Jiang et al. [134] reported significant downregulation of L-OPA1 expression in the lung tissues and alveolar epithelium of LPS-induced ALI mice. Inhibiting L-OPA1 expression exacerbated necroptosis in alveolar epithelial cells by inducing mitochondrial fragmentation and reducing the mitochondrial membrane potential. Suliman et al. [135] further confirmed that mitochondrial injury induces necroptosis in lung epithelial cells, thereby promoting ALI development. A recent study [136] demonstrated that mitochondrial citrate accumulation drives necroptosis of alveolar epithelial cells in LPS-induced ALI. Mechanistically, citrate directly binds to FUN14 domain-containing protein 1 (FUNDC1), facilitating its interaction with dynamin-related protein 1 (DRP1) and inducing autophagy-dependent necroptosis in alveolar epithelial cells [136]. Triggering receptor expressed on myeloid cells 1 (TREM-1), a pattern recognition receptor widely expressed on monocytes/macrophages, was reported by Zhong et al. [137] to induce necroptosis in alveolar macrophages through mTOR-dependent mitochondrial division, exacerbating inflammation and worsening ALI.

ALI is associated with various direct or indirect pathological factors, with necroptosis emerging as a key

contributor to its pathogenesis. In the renal–lung cascade of ALI, acute immune rejection postrenal transplantation and renal ischaemia–reperfusion injury are the primary instigators. Zhao et al. [138] reported significant increases in RIPK1 and RIPK3 expression in the lung tissues of rats with ALI following renal transplantation. Treatment with Nec-1, a RIPK1 inhibitor, reduced their expression, exerting a lung-protective effect. Elevated TNF-α and IL-1β levels are associated with pathological lung changes in renal transplant recipients [138]. TNF-α treatment in recipient rat lung and alveolar epithelial cells resulted in elevated expression of OPN, endoplasmic reticulum stress, and necroptosis, which were partially mediated by OPN. Exogenous OPN exacerbates ALI and necroptosis, whereas OPN-siRNA reduces ALI after kidney transplantation by mitigating endoplasmic reticulum stress, necroptosis, and the inflammatory response [139]. In a rat model of ALI induced significantly by hyperbaric oxygen exposure, oxidative stress promoted the expression of necroptosis markers, which were inhibited by Nec-1 intervention, alleviating lung pathology [140]. Plasma RIPK3 levels were elevated in ventilator-induced ALI patients, whereas RIPK3 deficiency, but not MLKL deficiency, ameliorated VILI in a mouse model [141]. VILI is correlated with impaired FAO and is significantly reduced in RIPK3-deficient mice, suggesting that FAO-dependent RIPK3-mediated necroptosis is a pathogenetic mechanism [141]. Plasma exosomal levels of APN/CD13 was elevated in sepsis-induced ALI patients and mouse models, which induced necroptosis in alveolar epithelial cells [142]. EGFR- and TNFR1-specific binding promoted increased NF-κB/MAPK-mediated inflammation in sepsis-induced ALI, inducing RIPK3-dependent necroptosis in alveolar epithelial cells [143]. Cardiopulmonary bypass (CPB) promoted ALI development by mediating the exosomal release of HMGB1 through the mtDNA/cGAS/STING pathway, inducing necroptosis in the alveolar epithelium [144]. Therefore, focusing on necroptosis may represent a novel therapeutic approach for ALI.

Necroptosis in infectious pneumonia

Pneumonia is a prevalent and severe infectious disease that significantly contributes to global morbidity and mortality, with an estimated three million deaths annually. In addition to its role in chronic lung ailments, emerging evidence indicates that necroptosis is a pivotal player in the pathophysiological mechanisms of infectious pneumonias such as COVID-19, exacerbating disease progression (Fig. 4).

Viral pneumonia

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-induced necrotizing apoptosis is considered pivotal in causing acute lung injury and the inflammatory cytokine storm in COVID-19 patients [145]. Ferren et al. reported necroptosis in both lung and brainstem tissues during infection with this novel coronavirus [146]. The envelope protein (E) of SARS-CoV-2 is crucial for viral assembly and pathogenesis, with Baral et al. [147] observing that the E protein mediates cellular inflammation and necroptosis through RIPK1. Hao et al. [148] demonstrated the critical role of necroptosis in polarization and epithelial barrier damage in human airway epithelial cells (HAECs) infected with SARS-CoV-2. Inhibiting necroptosis-related genes or processes can ameliorate the barrier function of disrupted HAECs. AT2 cells are pivotal in alveolar defence and play a significant reparative role in COVID-19. Schifanella et al. [149] reported that TNF-α-induced necroptosis and bruton tyrosine kinase (BTK)-induced pyroptosis collectively promote the death of AT2 cells and strong inflammatory responses, contributing to the unique pathology observed in COVID-19 development.

Influenza A virus (IAV), a lytic RNA virus, triggers receptor RIPK3-mediated apoptosis and MLKL-dependent necroptosis in infected cells. In IAV-induced mammalian fibroblasts and lung epithelial cells, IAV activates MLKL-driven necroptosis and FADD-mediated apoptosis through RIPK3, a cytolytic mechanism crucial for controlling respiratory IAV infection [150]. ZBP1 is pivotal in IAV-induced necroptosis, with IFNs, TNFα, and TLR3/4 agonists potently inducing ZBP1 expression in primary mouse alveolar epithelial cells. IAV infection induces intense necroptosis [151] by phosphorylating MLKL in infiltrating immune cells and alveolar epithelial cells. Zhang et al. [33] demonstrated that replicated IAVs produce Z-RNA, which interacts with nuclear ZBP1, initiating RIPK3-mediated MLKL activation, resulting in nuclear envelope disruption, cytoplasmic DNA leakage, and subsequent cell necroptosis. Compared with IAV-infected mice, *Mlkl*$^{-/-}$ mice exhibit reduced destruction of lung epithelial cell nuclei, decreased lung-infecting neutrophil counts, and improved survival rates [33]. Basavaraju et al. [152] reported that ZBP1-RIPK3 is crucial not only in IAV infection but also in SARS-CoV-2 and other viral infections. A recent study demonstrated that IFN-induced upregulation of the interferon-stimulating factor 2'-5'-oligoadenylate synthetase-like protein mitigates virus-induced necroptosis by inhibiting the RIPK3-ZBP1-MLKL signalling pathway, exerting an antiviral effect [153]. Ossifying proteins (OPNs) play crucial roles in regulating cell death and immunity. WANG et al. reported that OPN deficiency may protect mice from IAV infection by reducing macrophage necroptosis, thereby decreasing viral titres [154]. Recent studies have shown that inhibiting necroptosis induced by influenza

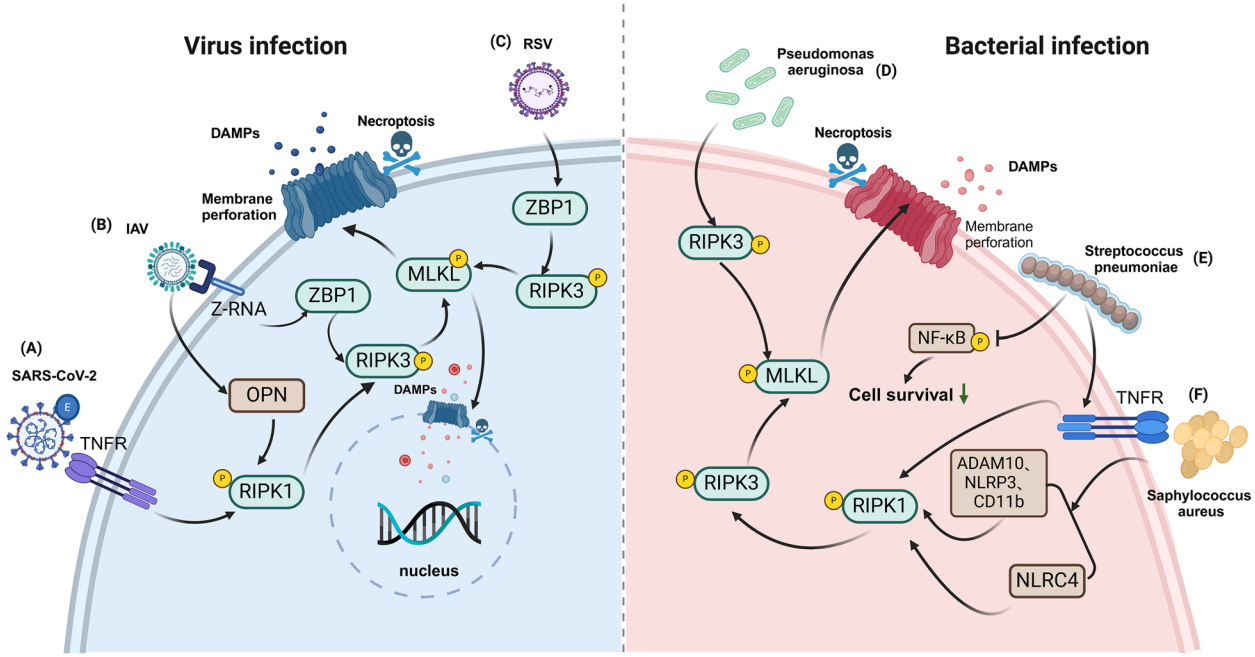

Fig. 4 Necroptosis in infectious pneumonia presents diverse mechanisms across different pathogens. **A** The envelope protein (**E**) of SARS-CoV-2 uniquely mediates necroptosis and inflammatory cytokine release via RIPK1, marking a distinct feature in COVID-19 pathogenesis. **B** Influenza A virus (IAV) employs Z-RNA to interact with ZBP1, initiating RIPK3-mediated necroptosis while also upregulating OPN expression, modulating necroptosis and immunity. **C** Respiratory syncytial virus (RSV) induces necroptosis through the RIPK1/RIPK3/MLKL pathway, with MLKL further promoting NETs formation, exacerbating airway inflammation. **D** Pseudomonas aeruginosa primarily triggers necroptosis via RIPK3, leading to lung inflammation and tissue damage. **E** Streptococcus pneumoniae triggers necroptosis via RIPK1/RIPK3/MLKL while inhibiting cell survival through NF-κB inhibition. **F** Staphylococcus aureus toxins target ADAM10, NLRP3, and CD11b or activate NLRC4, inducing immune cell necroptosis via the RIPK1/RIPK3/MLKL pathway, thus exacerbating respiratory diseases

virus infection in the lungs improves cardiac proteomic remodelling, thus reducing cardiac damage [155, 156].

Respiratory syncytial virus (RSV) infection induces necroptosis in primary mouse macrophages and human monocytes in a RIPK1/RIPK3/MLKL-dependent manner, reducing the viral clearance efficiency of alveolar macrophage. Compared with wild-type mice, *Ripk3*$^{-/-}$ mice infected with RSV exhibit a significantly lower lung viral load and less lung damage [157]. RIPK1 and MLKL expression increases in RSV-inoculated HAECs and neonatal mice, promoting necroptosis and shedding of HAECs, HMGB1 release, and neutrophilic inflammation. Inhibiting RIPK1 or MLKL alleviates these pathologies, reduces the viral load, and prevents type 2 inflammation and airway remodelling [158]. Additionally, RIPK1/RIPK3/MLKL is critical in RSV-induced neutrophil extracellular traps (NETs). MLKL promotes membrane perforation rupture, which is essential for RSV-induced NETs, leading to neutrophil lysis and content expulsion, exacerbating bronchial inflammation [159]. Therefore, necroptosis is a prominent cell death pathway triggered by RSV infection that is closely associated with RSV-driven tracheal inflammation and remodelling, and its immune and pathological downstream consequences warrant future research attention [160].

Bacterial pneumonia

Staphylococcus aureus, a bacterium commonly found on the skin and mucous membranes, is a virulent strain capable of inducing severe respiratory infections. Toxins produced by the *Staphylococcus aureus* USA300 strain primarily target ADAM10, NLRP3, and CD11b, thereby inducing necroptosis in human immune cells through the RIPK1/RIPK3/MLKL signalling pathway [161]. *Staphylococcus aureus* activates NLRC4 to facilitate neutrophil necroptosis and IL-18 production, consequently inhibiting IL-17 A-dependent neutrophil aggregation [162]. *Nlrc4*$^{-/-}$ mice display diminished rates of neutrophil necrosis along with increased recruitment and aggregation. Furthermore, either inhibiting necroptosis or genetically reducing MLKL and IL-18 can bolster defence against *Staphylococcus aureus* infection in wild-type mice [162]. Liu et al. [163] reported that the interferon-stimulated gene STING hampers *S. aureus* infection in the lung by impeding necroptosis. TNF-α significantly increases *Staphylococcus aureus*-induced LDH release,

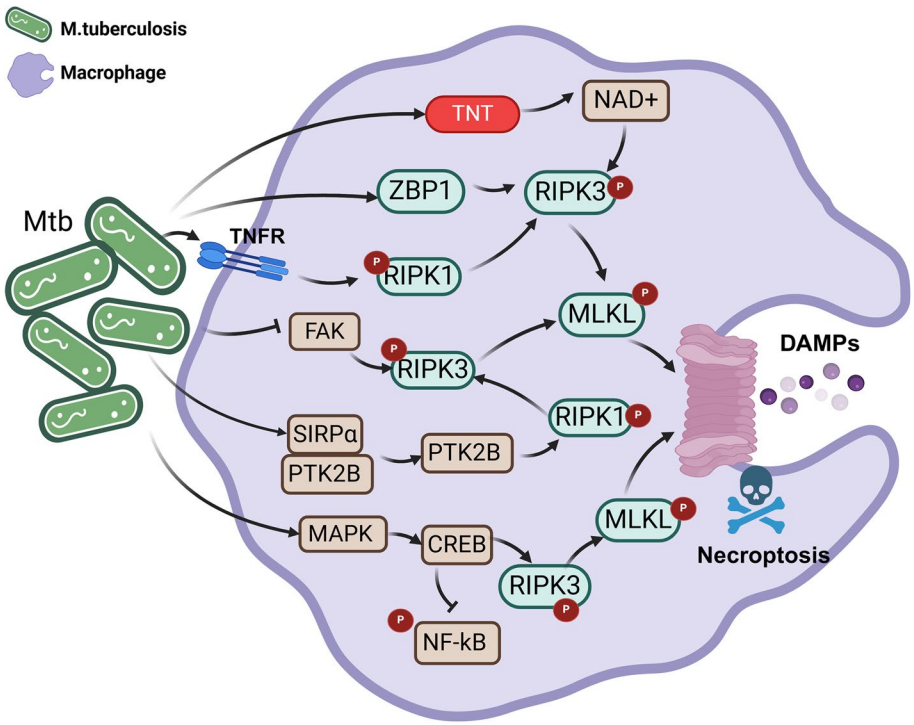

Fig. 5 Necroptosis in pulmonary tuberculosis (TB). Necroptosis of macrophages plays a pivotal role in TB pathology. Key insights reveal the involvement of tuberculous necrosis toxin (TNT) in triggering necroptosis and the impact of NAD + depletion on its induction, thus influencing TB pathology. Additionally, focal adhesion kinase (FAK), signal regulatory proteinα (SIRPα), and cAMP response element-binding protein (CREB) are crucial in orchestrating immune responses to Mtb infection, particularly by inhibiting necroptosis and regulating cellular signaling pathways

while infection of A549 lung epithelial cell lines with *Staphylococcus aureus* increases RIPK3 and cleaved caspase-1 protein levels, thereby promoting apoptosis and necroptosis in A549 cells [164]. In necroptosis mediated by TNF and TLRs and in *Staphylococcus aureus*-induced lung injury, RIPK1 and RIPK3 promote c-Jun N-terminal kinase (JNK1/2) activation and proinflammatory cytokine production in macrophages. Inhibiting JNK significantly curtails macrophage necroptosis [165].

Necroptosis is a predominant mechanism of cell death in bacterial pneumonia, with pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* capable of triggering immune cell death through the RIPK1/RIPK3/MLKL pathway [166]. Throughout bacterial pneumonia progression, pore-forming toxins from diverse bacterial strains serve as a shared mechanism, independently inducing necroptosis or in the absence of TNFR1, TNFR2, and TLR4 signals. This induces necroptosis in respiratory epithelial cells while simultaneously activating caspases, collectively exacerbating the proinflammatory effects of bacterial pneumonia [167, 168]. Alveolar macrophages initiate innate immune-mediated antibacterial defence in streptococcus pneumoniae pneumonia. Coleman et al. [169] reported that low NF-κB activation is a virulence trait in *Streptococcus pneumoniae*, worsening mouse lung infections by promoting macrophage necroptosis. Conversely, *Streptococcus pneumoniae*, which has high NF-κB activity, can reverse this effect by activating macrophages [169]. Additionally, *Streptococcus pneumoniae* can invade the myocardium, inducing cardiomyocyte necroptosis, leading to cardiac injury and scarring [170]. Moreover, *Aspergillus fumigatus* infection is an immune-related fatal condition in which intermacrophage calcium-dependent *Aspergillus fumigatus* transfer triggers fungal germination in late-stage phagosomes, inducing macrophage necroptosis, a key mechanism underlying aspergillosis pathology [171]. In a clinical model of *Pseudomonas aeruginosa* pneumonia, the RIPK3 scaffold drives lung inflammation and mortality. Inhibiting RIPK3 expression in *Pseudomonas aeruginosa*-infected mice suppresses necroptosis, thereby reducing inflammation and mitigating lung tissue damage [172].

Necroptosis in pulmonary tuberculosis

Mycobacterium tuberculosis (Mtb) causes pulmonary tuberculosis (TB), which is characterized by immune cell aggregation into granulomas, aiding in the spread of Mtb [173]. Modulating cell death responses is key in TB pathogenesis and influences host–Mtb interactions [174].

Macrophages, which are primary Mtb defenders and reservoirs, activate macrophage necroptosis (Fig. 5) [175]. Tuberculous necrosis toxin (TNT), a secreted nicotinamide adenine dinucleotide (NAD^+) glycohydrolase, prominently triggers necroptosis in Mtb-infected macrophages. NAD^+ depletion induced by TNT prompts the expression of RIPK3 and MLKL in infected macrophages, independent of TNF-α or RIPK1, which is associated with mitochondrial depolarization and impaired ATP synthesis [176]. Additionally, NAD^+ deficiency induces RIPK3 and MLKL expression, whereas NAD^+ restoration mitigates Mtb-induced pathology [176]. Butler et al. [177] further reported that macrophages infected solely with Mtb undergo RIPK3-dependent cell death, are devoid of p-MLKL, and are associated with mitochondrial ROS. The necroptosis of Mtb-infected macrophages facilitates microbial evasion and dissemination. Stutz et al. reported increased levels of intracellular MLKL, TNFR1, and ZBP1 and decreased levels of cIAP1 upon macrophage infection with Mtb, which establishes a robust pronecrotic environment [177]. However, the inhibition of MLKL or RIPK1 did not impact disease outcomes in murine models. Consequently, while Mtb triggers macrophage necrosis in parallel with the apoptotic pathway, the inhibition of necroptosis merely attenuates disease pathogenesis [178].

Mtb infection induces a time-dependent reduction in focal adhesion kinase (FAK) expression in human macrophages. Afriyie-Asante et al. [179] postulated that FAK constitutes a critical protective response during Mtb infection. Throughout Mtb infection, FAK predominantly mediates the RIPK1-dependent cell death mechanism, followed by the RIPK3-MLKL-dependent pathway [179]. Wang et al. [180] noted a correlation between signal regulatory protein α (SIRPα) levels and TB patient efficacy, suggesting that SIRPα is a novel TB biomarker. Mtb augments SIRPα expression in macrophages. SIRPα deficiency enhances macrophage antimicrobial activity against Mtb through increased autophagy and necroptotic inhibition [180]. The inhibition of necroptosis caused by SIRPα deficiency requires PTK2B activity, and the C-terminal domain of SIRPα directly interacts with PTK2B, inhibiting its activation in macrophages [180]. Consequently, SIRPα/PTK2B-mediated necroptosis in macrophages is a potential regulatory mechanism against Mtb. cAMP response element-binding protein (CREB), a transcription factor, orchestrates various cellular responses within macrophages. Mtb rapidly activates CREB in human macrophages via MAPK p38 signalling, promoting the expression of immediate early genes, including COX2, MCL-1, CCL8, and c-FOS, while impeding NF-kB nuclear translocation [181]. Further investigations revealed that CREB restricts phagolysosomal fusion by inhibiting the necroptotic pathway, with CREB inhibition leading to RIPK3 and MLKL phosphorylation without significant cell death [181].

Translation from bench to bedside

Small molecule inhibitors

Researchers have developed inhibitors targeting the necroptosis pathway, including RIPK1, RIPK3, and MLKL inhibitors, which have demonstrated promising therapeutic effects in preclinical models of respiratory system diseases (Table 1). Nec-1, a inhibitor of RIPK1, binds to the hydrophobic pocket formed by the carboxyl and amino-terminal segments of the RIPK1 kinase domain, exhibiting favourable therapeutic effects in preclinical studies of diseases such as COPD [80], lung ischaemia–reperfusion injury [182], IPF [100], and ALI [183]. Additionally, GSK2982772, an emerging RIPK1 inhibitor, directly binds to RIPK1, displaying high kinase activity and effectively blocking TNF-induced necroptosis [184]. In vivo experiments revealed that the RIPK1 inhibitor GSK2982772 protected against LPS-induced lung injury in mouse models, with reduced neutrophil and monocyte infiltration in the lungs [185]. PK-68 is a

Table 1 Small molecule inhibitors of necroptosis in respiratory diseases

Categories	Drug	Diseases	References
RIPK1 inhibitor	Necrostatin-1	COPD, lung ischemia-reperfusion injury, IPF, and ALI.	[80, 100, 182, 183]
	GSK2982772	ALI	[184]
	PK68	NSCLC	[186]
RIPK3 inhibitor	GSK-872	Influenza	[150]
	HS-1371	NSCLC	[188]
	Dabrafenib	NSCLC	[189]
	UH15-38	Severe influenza	[190]
	HG-9-91-01	Staphylococcus aureus pneumonia	[191]
MLKL inhibitor	Necrosulfonamide	Lung ischemia-reperfusion injury, Bacterial pneumonia	[192, 193]

novel RIPK1 inhibitor synthesized by Chinese scientists. Importantly, PK68 provides strong protection against lung cancer in vivo [186]. Moreover, Zharp1-211, another RIPK1 inhibitor developed by researchers, significantly attenuates inflammatory damage in graft-versus-host disease [187]. These collective findings provide renewed optimism for the treatment of respiratory system diseases. GSK-872, a selective inhibitor of RIPK3 kinase, was demonstrated by Nogusa et al. [150] to significantly inhibit necroptosis of lung epithelial cells induced by influenza A virus infection. HS-1371, a novel RIPK3 inhibitor, binds to the ATP-binding pocket of RIPK3, inhibiting its enzymatic activity in vitro [188]. Furthermore, dabrafenib, a B-RafV600E inhibitor, mitigates acetaminophen-induced liver injury by selectively inhibiting RIPK3, thereby offering insights into the treatment of respiratory system diseases [189]. Gautam et al. [190] recently introduced UH15-38, a pioneering RIPK3 inhibitor. This compound selectively hinders IAV-induced necroptosis within alveolar epithelial cells in vivo. Moreover, UH15-38 has the capacity to mitigate lung inflammation and avert mortality subsequent to infection with both laboratory-adapted and pandemic strains of IAV [190]. Notably, these effects occur without detriment to antiviral adaptive immune responses or hindrance of viral clearance. Huang et al. reported that HG-9-91-01 inhibits RIPK3 enzyme activity, safeguarding mice against *Staphylococcus aureus*-induced lung injury by specifically targeting the kinase activity of RIPK3 [191]. Phosphorylated MLKL, a crucial executor of necroptosis, underscores the importance of targeting MLKL to inhibit necroptosis. Necrosulfonamide selectively targets MLKL, inhibiting the interaction between MLKL-RIPK1-RIPK3 necrosomes and their downstream effectors [9]. Additionally, Ueda et al. [192] reported that necrosulfonamide significantly improves lung ischaemia–reperfusion injury by inhibiting necroptosis in mice. Furthermore, necrosulfonamide ameliorates lung tissue damage caused by methicillin-resistant *Staphylococcus aureus* infection by inhibiting neutrophil necroptosis induced by phenol-soluble modulin [193].

Natural products

Natural sources serve as crucial reservoirs for identifying novel therapeutic compounds. As shown in Table 2, natural compounds can modulate necroptosis and thereby offer therapeutic benefits for respiratory conditions. Eleutheroside B, a natural polyphenolic compound derived from *Acanthopanax senticosus*, has a spectrum of pharmacological activities, including anti-inflammatory, antioxidant, and antidepressant effects. Wang et al. [194] administered eleutheroside B to rats at doses of 50 mg/kg and 100 mg/kg in a model of high-altitude pulmonary oedema. The results indicated significant mitigation of pulmonary oedema in rats, along with reduced levels of inflammatory mediators such as TNF-α and IL-1β in bronchoalveolar lavage fluid. Further investigations revealed the capacity of eleutheroside B to mitigate oxidative stress and suppress necroptosis in alveolar epithelial cells through the activation of Nrf2 transcriptional activity. Crocetin, an active constituent extracted from *Crocus sativus L.*, has been shown to effectively ameliorate radiation-induced thickening of alveolar walls and destruction of alveoli by downregulating the transcription of the Tnfrsf10b gene, thereby inhibiting activation of the RIPK1/RIPK3/MLKL necroptosis signalling pathway [195]. These findings present a novel approach for mitigating lung radiation injury by the use of herbal extracts. Aloperine, a bioactive alkaloid isolated from *Sophora flavescens Aiton*, has diverse biological effects, including anti-inflammatory, immunomodulatory, and antioxidant properties. A recent study demonstrated that aloperine can attenuate lung tissue damage and inflammation in LPS-induced ALI mice by inhibiting

Table 2 Natural compounds targeting necroptosis for intervention in respiratory diseases

Drug	Diseases	Targets	References
Eleutheroside B	High-altitude pulmonary oedema	Nrf2↑ RIPK1↓ RIPK3↓ MLKL↓ necroptosis and oxidative stress↓	[194]
Crocetin	Acute radiation-induced lung injury	Tnfrsf10b↓ RIPK1↓ RIPK3↓ MLKL↓ necroptosis↓	[195]
Aloperine	Acute lung injury	RIPK1↓ RIPK3↓ MLKL↓ NF-κB↓ necroptosis↓	[183]
Cryptotanshinone	NSCLC	RIPK1↑ RIPK3↑ MLKL↑ ROS↑ necroptosis↑	[196]
Tanshinol A	NSCLC	RIPK3↑ MLKL↑ ROS↑ necroptosis↑	[197]
Isobavachalcone derivatives	NSCLC	RIPK1↑ RIPK3↑ MLKL↑ ROS↑ necroptosis↑	[198]
Theaflavin-3,3′-digallate	COPD	p38 MAPK↑ RIPK1↓ RIPK3↓ MLKL↓ necroptosis↓	[199]
Apigenin	Mycoplasma pneumonia	PPARγ↑ Uhrf1↑ TNF-α↓ RIPK1↓ RIPK3↓ MLKL↓ necroptosis↓	[200]
Ursolic acid	Pulmonary tuberculosis	TNF-α↓ TNFR↓ RIPK1↓ RIPK3↓ MLKL↓ necroptosis↓	[201]

necroptosis [183]. Consistently, in vitro studies have indicated that aloperine significantly suppresses the levels of p-RIPK1, p-RIPK3, p-MLKL, and p-NF-κB proteins and NF-κB nuclear translocation while also reducing IL-8 and IL-12 levels in LPS-stimulated mouse lung epithelial cells. Cryptotanshinone, a diterpene quinone compound derived from *Salvia miltiorrhiza*, has been previously noted for its significant anticancer activity [196]. Recent investigations revealed its capacity to induce necroptosis in lung cancer A549 cells by promoting the activation of the RIPK1/RIPK3/MLKL signalling pathway, thus revealing a novel anticancer mechanism. Tanshinol A, another natural compound derived from *Salvia miltiorrhiza*, was reported by Zhang et al. to induce nonclassical necroptosis mediated by MLKL in A549 lung cancer cells by increasing reactive oxygen species generation [197]. Furthermore, Chen et al. [198] demonstrated that a novel derivative of isobavachalcone, Compound 16, induced necroptosis in H1975 NSCLC cells. Curcumin-3-O-methoxyphenol ester, an active constituent of turmeric, has been demonstrated in both in vitro and in vivo studies to significantly alleviate lung tissue damage and inflammation in COPD mice by modulating the p38 MAPK/RIPK3/MLKL signalling pathway, thereby increasing the antioxidant capacity of lung tissue [199]. Recently, Mei et al. [200] reported that apigenin reduces alveolar macrophage necroptosis through the PPARγ/Uhrf1/TNF-α pathway, potentially influencing the treatment of *Mycoplasma pneumoniae*. Ursolic acid can mitigate the overactive inflammatory reaction triggered by macrophages infected with Mtb by inhibiting necroptosis in macrophages and adjusting the host immune response via the TNF-α/TNFR signalling pathway [201].

Clinical studies

The development of clinical therapeutic agents targeting the necroptosis signalling pathway is essential for treating respiratory system diseases. The RIPK1 inhibitor GSK2982772, which was demonstrated to be safe and well tolerated in a phase I trial [202], has been tested in phase II trials for various diseases, including ulcerative colitis [203] and rheumatoid arthritis [204]. Furthermore, a phase Ib clinical study revealed that the RIPK1 inhibitor eclitasertib (SAR443122) demonstrated good tolerability compared with a placebo. Additionally, a consistent trend towards faster resolution of inflammatory biomarkers and clinical improvement was observed in patients with severe COVID-19 than in the placebo group [205]. SAR443820 has been reported to penetrate the cerebrospinal fluid after oral administration and exert therapeutic effects in patients with Alzheimer's disease and amyotrophic lateral sclerosis by reducing the phosphorylation of RIPK1 at serine 166 in human peripheral blood mononuclear cells [206]. Although RIPK3 inhibitors and MLKL inhibitors have demonstrated therapeutic effects on respiratory system diseases in preclinical models, no corresponding drugs have yet entered clinical trials.

Limitations and considerations for future research directions

Limited direct evidence supports the role of necroptosis in human pulmonary tissue. Additionally, our understanding of the dynamic changes induced by necroptosis in pulmonary diseases in humans is inadequate, even in scenarios where necroptosis is presumed to occur. This deficiency arises predominantly from evidence obtained in rodent studies. Consequently, there are significant challenges in translational research regarding necroptosis in pulmonary diseases. First, the experimental conditions applied to animal models often fail to adequately reflect clinical situations and cannot fully elucidate the intricate pathophysiological interactions within patients. For example, the use of hypoxia-induced PH animal models does not effectively simulate the characteristic pulmonary arterial remodelling observed in patients with PH. Second, despite remarkable anatomical and molecular similarities between mice and humans, differences exist in immunological and cellular death pathway components. Notably, humans express caspase-4, -5, and −10, whereas mice express caspase-11 exclusively. Moreover, the autophosphorylation site of human RIPK3 is S227, whereas in mice, it is T231/S232. These distinctions underscore the necessity for caution when extrapolating results from animal studies to human research endeavors. These challenges underscore our inability to extrapolate precise clinical contexts wherein the modulation of necroptotic pathways could confer benefits to human health. Hence, there is a need to elucidate more precisely the role and mechanisms of necroptosis in human pulmonary diseases. Given the diverse PTMs of key effector proteins involved in necroptosis, mass spectrometry analysis could comprehensively reveal protein secretion and phosphorylation events during TNF-induced necroptosis, thereby increasing the sensitivity of necroptosis detection. Zu et al. [207] utilized mass spectrometry to quantitatively assess the temporal dynamics of more than 7,000 confidently identified phosphorylation sites throughout the course of necroptosis. This research revealed that oligomerized MLKL initiates the activation of p38 MAPK, consequently facilitating the phosphorylation of RIPK1 S473, thereby mediating inflammation during the latter stages of necroptosis.

While inhibitors of necroptosis have exhibited favourable therapeutic effects in acute infectious lung diseases such as COVID-19, the primary limitation in

translational research on necroptosis in chronic lung diseases revolves around the ambiguity regarding the timing of necroptosis initiation. For example, the specific onset of necroptosis in chronic lung conditions such as COPD remains unidentified, posing a significant impediment to the clinical implementation of necroptosis inhibitors. The utilization of cutting-edge technologies, such as single-cell omics and spatial transcriptomics, has the potential to clarify the cellular dynamics involved in necroptosis across different stages of diverse lung diseases. Additionally, these methodologies offer insights into the novel mechanisms governing the signalling pathways associated with necroptosis. These investigative endeavors are anticipated to augment the existing in vivo evidence base pertaining to necrosis in human pulmonary ailments. Chan et al. [208] used single-cell sequencing to discern a distinctly destructive, immunosuppressive monocyte/macrophage subset within the tumours of SCLC patients and demonstrated a positive correlation with recurrent metastasis in these patients. Van Eeckhoutte et al. [80] utilized single-cell RNA sequencing to evaluate RIPK1 expression levels in the lungs of patients with COPD. Their investigation revealed a substantial increase in RIPK1 protein expression across AT1, AT2, and neuroendocrine cells among COPD patients in comparison to both never-smokers and smokers without airflow limitation.

Moreover, necroptosis often occurs with other forms of PCD, such as pyroptosis, and cannot be considered in isolation. As a result, the mechanisms governing necroptosis in pulmonary diseases are typically intricate and variable. For example, in 2019, Malireddi et al. [209] introduced the concept of PANoptosis, a form of inflammatory cell death characterized by the essential features of cellular pyroptosis, apoptosis, and/or necrotic apoptosis, which is regulated by PANoptotic bodies. Additionally, autophagy and ferroptosis frequently instigate necroptosis in diverse lung cell populations. Consequently, the potential benefits of targeted therapies involving multiple pathways for complex diseases, such as acute and chronic pulmonary illnesses, warrant further investigation.

Discussion

This review systematically summarizes recent advancements in comprehending the intricate roles of necroptosis in respiratory diseases. The pathogenesis of respiratory ailments is notably complex and involves extensive interactions among the cellular and organ systems. Mounting evidence underscores the intricate association between the necroptotic signalling cascade and diverse cell types implicated in respiratory conditions, including macrophages, AT1 cells, AT2 cells, airway epithelial cells, and endothelial cells. Although the necroptotic pathway has emerged as an attractive therapeutic target, its effective and safe modulation poses multifaceted challenges. Future research should prioritize exploring the occurrence and regulatory mechanisms of necroptosis across different cell types in various pulmonary disorders, thereby identifying precise intervention strategies. Given the diverse PTMs observed in RIPK1, RIPK3, and MLKL, future investigations should utilize techniques such as mass spectrometry and multiomics approaches to reveal novel modification patterns and sites, thus facilitating the development of innovative therapeutic modalities. Furthermore, the interplay between necroptosis and other forms of PCD assumes a pivotal role in the pathophysiological cascades of respiratory diseases. Consequently, the development of multitarget inhibitors or combination therapies is warranted to address the intricate alterations observed in clinical settings, thereby augmenting clinical efficacy. Notably, the current clinical research landscape regarding necroptosis inhibitors in respiratory diseases remains limited. Hence, future collaborative endeavors between clinicians and researchers are imperative to propel additional clinical investigations and provide improved evidence-based medical treatments.

In summary, this review meticulously delineates the multifaceted roles of necroptosis in respiratory pathogenesis, highlighting the need for targeted and nuanced therapeutic interventions to advance the clinical management of respiratory diseases.

Abbreviations

AECs	airway epithelial cells
ALI	acute lung injury
AT1	type I alveolar epithelial cell
CHOP	C/EBP homologous protein
CK	casein kinase
COPD	chronic obstructive pulmonary disease
CREB	cAMP response element-binding protein
CS	cigarette smoke
DAMPs	damage-associated molecular patterns
FADD	fas-associated death domain protein
IFNs	Interferons
IAV	influenza A virus
IL	interleukin
IPF	idiopathic pulmonary fibrosis
JAK1	Janus kinase 1
L-OPA1	long optic atrophy protein 1
LPS	lipopolysaccharide
LUAD	lung adenocarcinoma
MAPK	mitogen-activated protein kinase
MLKL	mixed-lineage kinase domain-like protein
NAD^+	nicotinamide adenine dinucleotide
NLRP3	NOD-like receptor protein 3
NF-κB	nuclear factor kappa B
NSCLC	non-small cell lung cancer
OPNs	ossifying proteins
PCD	programmed cell death
PH	pulmonary hypertension
PTMs	post-translational modifications
RHIM	RIP homotypic interaction motif
RIPK1	receptor-interacting serine/threonine protein kinase 1
RIPK3	receptor-interacting serine/threonine protein kinase 3

RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRPα	signal regulatory proteinα
STAT1	signal transducer and activator of transcription 1
SUMO	small ubiquitin-like modifier
TB	tuberculosis
TLRs	toll-like receptors
TNFR	tumor necrosis factor receptor
TRADD	TNFR1-associated death domain protein
TRADD	tumor necrosis factor receptor-associated factor
ZBP1	Z-DNA binding protein 1

Acknowledgements
The authors acknowledg the BioRender (www.biorender.com), as figures in this review were created with the BioRender platform.

Authors' contributions
X. C. searched the literature and drafted the manuscript. A. D. and J. L. conceived and designed the review. R. Z., F. W., L. Z., J .Y., R. Y., Qi. D. and L. S. examined the literature and made the figures. J. T., A. D. made a critical revision of the review. All authors contributed to the article and approved the submitted version.

Funding
This work was supported by the National Natural Science Foundation of China (82370069), the Natural Science Foundation of Hunan Province (2021JJ30017), the Hunan Scientific Research Program of traditional Chinese Medicine (C2022001), and the Postgraduate Scientific Research Innovation Project of Hunan Province (CX20230792).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Received: 20 June 2024 Accepted: 22 August 2024
Published online: 28 August 2024

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