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Biological and pharmacological roles of pyroptosis in pulmonary inflammation and fibrosis: recent advances and future directions

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Abstract

Pyroptosis, an inflammatory regulated cell death (RCD) mechanism, is characterized by cellular swelling, membrane rupture, and subsequent discharge of cellular contents, exerting robust proinflammatory effects. Recent studies have significantly advanced our understanding of pyroptosis, revealing that it can be triggered through inflammasome- and caspase-independent pathways, and interacts intricately with other RCD pathways (e.g., pyroptosis, necroptosis, ferroptosis, and cuproptosis). The pathogenesis of pulmonary fibrosis (PF), including idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases, involves a multifaceted interplay of factors such as pathogen infections, environmental pollutants, genetic variations, and immune dysfunction. This chronic and progressive interstitial lung disease is characterized by persistent inflammation, extracellular matrix (ECM) accumulation, and fibrotic alveolar wall thickening, which potentially contribute to deteriorated lung function. Despite recent advances in understanding pyroptosis, the mechanisms by which it regulates PF are not entirely elucidated, and effective strategies to improve clinical outcomes remain unclear. This review strives to deliver a comprehensive overview of the biological functions and molecular mechanisms of pyroptosis, exploring its roles in the pathogenesis of PF. Furthermore, it examines potential biomarkers and therapeutic agents for anti-fibrotic treatments.

Keywords Pulmonary fibrosis, Pyroptosis, Inflammation, Gasdermin, Inflammasome

Introduction

Pulmonary fibrosis (PF) is a chronic, inflammatory, progressive fibrotic lung disease characterized by respiratory difficulties, restrictive ventilatory impairment, gas exchange dysfunction, hypoxemia, and potentially progressing to respiratory failure [1]. Idiopathic pulmonary fibrosis (IPF) is a common type of PF, characterized by an unknown etiology, and is more prevalent in males aged 65 and older than in younger individuals [2, 3]. It is noteworthy that PF has been identified as a prominent long-term sequela of patients who experienced moderate or severe COVID-19 [4]. PF is universally progressive and

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carries a poor prognosis with a median survival time of 3.8 years post-diagnosis [5]. Currently, the U.S. FDA has approved nintedanib and pirfenidone as potential treatments for IPF. Although these drugs can delay the decline in lung function and improve progression-free survival in IPF patients, they do not significantly reduce the overall mortality rate or acute exacerbations [6, 7]. Aside from lung transplantation, there are no existing interventions that can significantly modify the progressive course of PF [8]. Therefore, further research is imperative to elucidate the pathogenesis of PF and to discover novel therapeutic targets and pharmacological agents.

It is recognized that PF can be triggered by multiple factors, including aging, chronic inflammation, tobacco smoke exposure, silica dust inhalation, gastroesophageal reflux, viral and bacterial infections, immune disorders, and genetic variation, which culminate in an uncontrolled reparative injury to the lungs [9–12]. Notably, the persistent pulmonary inflammatory response and the release of pro-fibrotic cytokines are recognized as precursors to fibrosis [13]. Pyroptosis is a novel inflammasome-driven lytic form of regulated cell death (RCD), characterized by the liberation of pro-inflammatory mediators upon cellular demise, thereby eliciting a robust inflammatory reaction [14]. This inflammatory RCD mechanism also plays a critical role in the innate immune response by facilitating the elimination of pathogens and impeding the replication of intracellular pathogenic microorganisms [15]. The principal characteristics of pyroptosis include cytoplasmic swelling, plasma membrane perforation, and the secretion of inflammatory mediators [16]. Current research indicates that pyroptosis can occur through several distinct pathways: the canonical pathway, the non-canonical pathways, the caspase-3/8-mediated pathway, and the granzyme-mediated pathway [17–20]. Notably, emerging evidence has demonstrated the pivotal role of gasdermin (GSDM) family proteins as essential effectors in mediating pyroptosis. In 2015, Shi and colleagues identified and elucidated the protein GSDMD as the target of inflammatory caspase-1, 4, 5, and 11, acting as the terminal pyroptotic executioner due to its pore-forming activities [21]. This discovery has greatly expanded our understanding of pyroptosis, which is now acknowledged as an inflammatory RCD form driven by gasdermins. Further mechanistic studies have unveiled that other gasdermin proteins, including GSDMA, GSDMB, GSDMC, and GSDME/DFNA5, exhibit membrane-disrupting capabilities similar to those of GSDMD [22–24]. Caspase-1, in its active form, cleaves the Asp275 site on GSDMD, generating an N-terminal fragment (GSDMD-NT) that initiates pyroptotic pore assembly in cellular membranes [25]. Subsequently, this process results in the efflux of cellular contents, interleukin (IL)-1β/18 release, and induces a proinflammatory response [26]. It is noteworthy that GSDMD can also trigger lysis of the mitochondrial membranes. According to a recent study, GSDMD-NT rapidly disrupted both inner and outer mitochondrial membranes, resulting in a decrease in mitochondrial numbers, dissipation of the transmembrane potential, and liberation of mitochondrial DNA (mtDNA) from the matrix and intermembrane space [27]. This indicates that GSDMD can punch holes not only in the cell membrane but also in the organelle membranes, thereby intensifying the pyroptotic response through the release of intracellular contents.

Mounting evidence suggests that pyroptosis plays a crucial role in driving inflammation during the onset and progression of PF [28, 29]. Nevertheless, the precise mechanism of pyroptosis in this devastating disease remains incompletely understood. This review offers a comprehensive overview of the molecular mechanisms of pyroptosis and its involvement in the pathogenesis of PF. Finally, building upon existing advancements in the field, prospective pyroptosis-targeting interventions for the treatment of PF and future research directions will also be discussed.

Overview of pyroptosis and its signal transduction

The recognition of pyroptosis traces back to 1992, when Zychlinsky et al. first observed macrophages exhibiting self-destructive behavior after being infected with *Shigella flexneri* [30]. Nonetheless, during that period, it was inaccurately classified as morphological alterations in caspase-1-mediated apoptosis. Nine years later, in 2001, following the observation of a similar *Salmonella typhimurium*-induced macrophage death, this novel caspase-1-dependent RCD was designated as pyroptosis [31]. In recent years, with the progress of several groundbreaking studies, we have gained a deeper understanding of the specific mechanisms of pyroptosis. Pyroptosis has been identified in diverse cell types, such as macrophages, stromal cells, endothelial cells, and alveolar epithelial cells (AECs) [32–34]. Evidence suggests that pyroptosis is initiated by pathogenic microorganisms or other threat signals and accompanied by a robust inflammatory reaction [35]. Molecularly, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) are initially detected intracellularly by cytoplasmic pattern recognition receptors (PRRs), leading to the activation of the inflammasome complex and the maturation of inflammatory caspases [36]. Then active caspase-1 cleaves the gasdermin, and the cell membrane progressively ruptures to generate 10–14 nm holes [16, 37]. Subsequently, lactate dehydrogenase (LDH), inflammatory factors, high-mobility group box protein 1 (HMGB1), and other intracellular contents are released extracellularly [37].

Gasdermin: the executioner of pyroptosis

Gasdermins constitute a family of evolutionarily conserved proteins present in various cells and tissues [38]. Accumulating evidence suggests that gasdermin proteins, the key mediators of pyroptosis, act as the ultimate executors of diverse and interconnected biological events [39]. Noteworthy, gasdermin proteins also play a role in regulating the inflammatory response and the pathophysiology of various chronic disorders, such as chronic respiratory diseases, rheumatic diseases, cardiovascular diseases, and PF [28, 32, 40, 41]. Nowadays, the comprehension of pyroptosis has progressed from its initial designation as caspase-1-mediated RCD to gasdermin-mediated RCD. In humans, the gasdermin family comprises six homologous genes: GSDMA/B/C/D/E and pejvakin.

GSDMA is the first characterized gene in the gasdermin family. The human genome encodes one form of GSDMA, whereas there are three GSDMA homologs (GSDMA1, GSDMA2, and GSDMA3) in mice [22]. Consistent with its expression in the skin, mutations of mouse GSDMA3 are implicated in diseases characterized by aberrant hair follicle development and alopecia, whereas polymorphisms in human GSDMA are associated with various disorders such as tumors and asthma [42, 43]. Additionally, a recent study has unveiled GSDMA as one of the susceptibility genes associated with systemic sclerosis [44]. In 2022, Deng and colleagues discovered that GSDMA undergoes specific cleavage by the group A streptococcus cysteine protease SpeB at Gln246, which triggers keratinocyte pyroptosis and enhances skin antimicrobial defence [24]. However, further research is warranted to ascertain the potential of other proteases for activating GSDMA.

GSDMB is the sole member of the gasdermin proteins uniquely expressed in humans [45]. Similar to GSDMA, GSDMB is also implicated in autoimmune disorders such as irritable bowel disease (IBD) and early-onset asthma [46, 47]. In several cancer cell lines, the upregulation of GSDMB by interferon-γ sensitized the cells to cytotoxic lymphocyte-mediated pyroptosis. Furthermore, the specific cleavage of GSDMB by cytotoxic lymphocytes (CTLs) or natural killer (NK) cells-derived granzyme A (GzmA) to generate GSDMB-NT induces pyroptosis and enhances the efficiency of immune checkpoint blockade in mouse tumor models [48]. These findings indicate that GSDMB overexpression may induce tumor clearance by triggering pyroptosis.

GSDMC was initially identified as a tumor-associated gene with elevated expression levels observed in various tissues, including the esophagus, spleen, stomach, and colon [49, 50]. Nevertheless, the biological function of GSDMC remains a subject of controversy. Its expression is downregulated in colorectal cancer, esophageal cancer, and breast cancer cells, yet it is upregulated in metastatic melanoma cells. Of note, GSDMC has been identified as a substrate of apoptotic caspase-8. Under hypoxic conditions, programmed death-ligand 1 (PD-L1) interacts with phosphorylated STAT3 to modulate GSDMC transcription [51]. Subsequently, metabolite alpha-ketoglutarate (α-KG) or tumor necrosis factor alpha (TNF-α) activating caspase-8 selectively splits GSDMC at Asp365 to generate GSDMC-NT and induces a transition from apoptosis to pyroptosis in cancer cells [19].

GSDMD is recognized as a pivotal gasdermin involved in inflammasome biology and the execution of pyroptosis [21]. Notably, GSDMD plays a critical role in defense against intracellular pathogens, cellular disturbances, and tumors [52, 53]. After being cleaved by inflammatory caspases (caspase-1, 4, 5, and 11), GSDMD-NT is liberated [21]. Subsequently, this domain binds to the inner leaflet of the plasma membrane and undergoes conformational changes, resulting in the formation of a transmembrane β-barrel that anchors firmly to the membrane [21]. Increasing evidence implicates that GSDMD is indispensable in the pathogenesis of pulmonary inflammation and fibrosis [54, 55]. Song et al. discovered that a specific upregulation of GSDMD in macrophages from murine and human silicosis lungs [56]. Moreover, inhibition of GSDMD-mediated pyroptosis in macrophages mitigates the advancement of pulmonary inflammation and fibrosis induced by silica [56]. Consistent with the aforementioned findings, another study demonstrates that knockdown of GSDMD inhibits silica-induced macrophage pyroptosis and attenuates the upregulation of fibrosis markers in fibroblasts, highlighting the crucial role of GSDMD-mediated pyroptosis in myofibroblast activation during the progression of silica-induced PF [57]. Consequently, studies aimed at inhibiting pyroptosis through targeting GSDMD signaling hold significant implications for the therapeutic management of fibrotic diseases.

Recent genetic association studies have unveiled the implication of GSDME in multiple diseases such as hereditary hearing loss, kidney diseases, acute lung injury, peritoneal fibrosis, and malignancies [58, 59]. Notably, GSDME plays a vital role in mediating the interplay between caspase-3-dependent apoptosis and pyroptosis. As the substrate of caspase-3, GSDME acts as a pivotal 'transducer' by redirecting cellular fate from apoptosis to pyroptosis, leading to a proinflammatory outcome [20]. The serine protease granzyme B, secreted by CTLs and NK cells, splits GSDME at an identical site to caspase-3. Owing to its unique expression and methylation characteristics across various tumors, GSDME shows promise as a biomarker for early detection [60]. Nevertheless, GSDME-mediated pyroptosis is also responsible for the toxicity and adverse effects associated

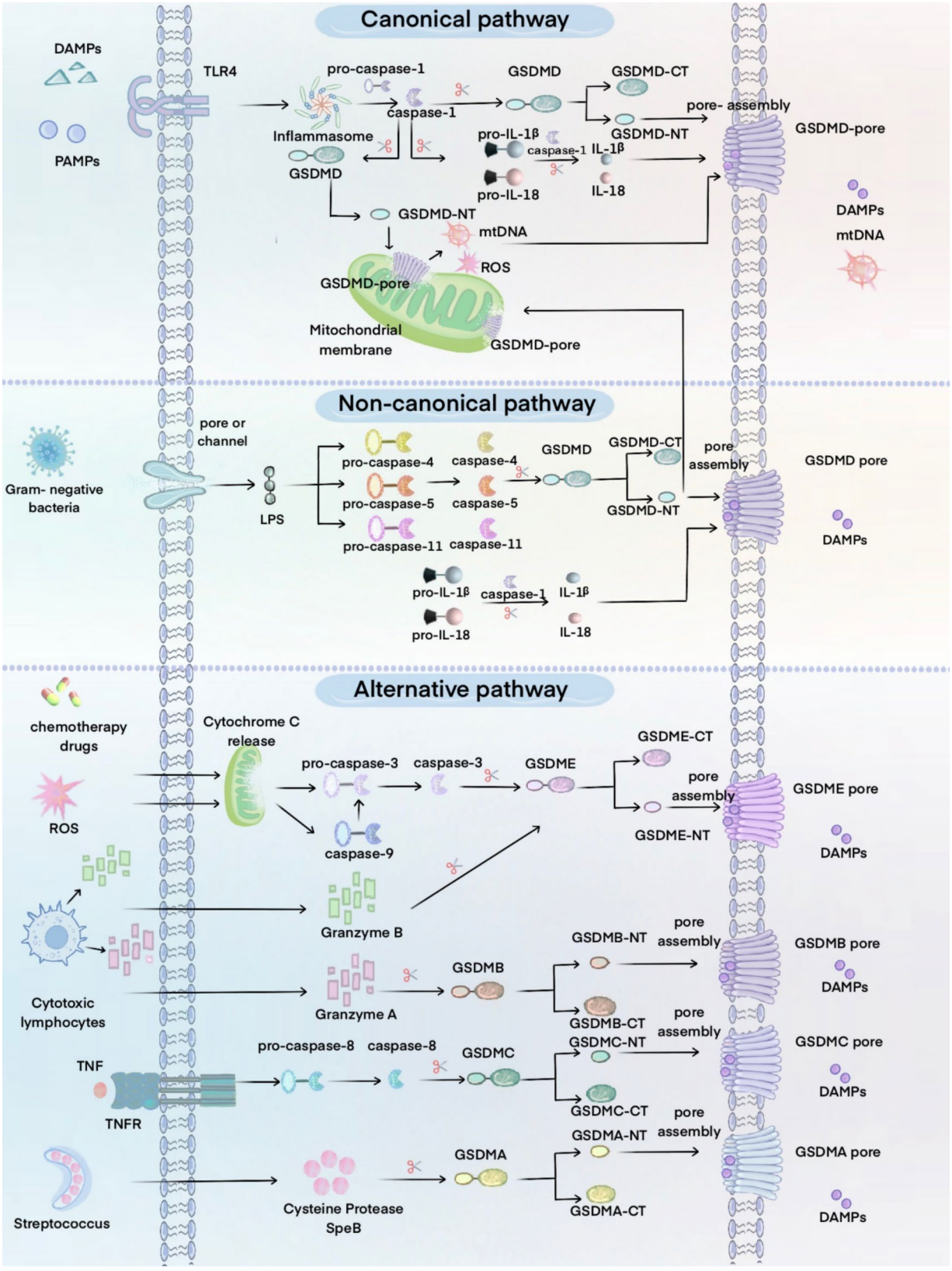

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Fig. 1 Schematic of pyroptosis signaling pathways. The canonical pathway initiates when PRRs detect PAMPs or DAMPs, triggering inflammasome assembly and caspase-1 activation, which cleaves GSDMD to release its N-terminal domain. Simultaneously, caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms, IL-1β and IL-18, respectively. GSDMD-NT then binds to the plasma membrane, forming pores that facilitate the secretion of IL-1β and IL-18, leading to cell swelling and membrane rupture. In the non-canonical pathway, LPS from Gram-negative bacteria activates caspase-4/5/11, triggering pyroptosis by cleaving GSDMD. GSDMD-NT also disrupts both inner and outer mitochondrial membranes, releasing mtDNA, mtROS, and proteins from the matrix and intermembrane space. Through alternative pathways, chemotherapy drugs or ROS can induce pyroptosis via the caspase-3/GSDME axis, independent of inflammasome assembly. Granzyme B from natural killer and $CD8^+$ T cells can directly cleave GSDME or activate caspase-3 to generate GSDME-NT, thus promoting pyroptosis. Additionally, caspase-1 or granzyme A cleaves GSDMB, while caspase-8 mediates GSDMC cleavage under hypoxia. In a separate pathway, Streptococcal pyrogenic exotoxin B induces pyroptosis through GSDMA cleavage

with certain chemotherapeutic drugs [20]. Additionally, GSDME plays a crucial regulatory role in pulmonary disorders and fibrosis diseases [61]. Wei et al. found that baicalin could effectively suppress influenza A (H1N1)-induced pyroptosis of lung AECs via the caspase-3/GSDME pathway [62]. According to a recent study, the NLRP1 inflammasome functions as a sensor of SARS-CoV-2 infection in lung epithelial cells, which ignites cell death via the GSDME-mediated pyroptotic pathway [63]. However, the role of GSDME-mediated pyroptosis in the development of PF remains elusive.

Pejvakin, a non-canonical gasdermin, is characterized by a divergent shorter C-terminal domain and the lack of an identifiable cleavable linker domain [64]. It is predominantly expressed in the inner ear, brain, liver, and testis, with a primary role in auditory maintenance [65, 66]. Recessive mutations in pejvakin result in impaired peroxisome homeostasis, rendering cochlear cells susceptible to noise-induced oxidative stress [65]. Furthermore, another study demonstrated that the R183W variant of pejvakin induces nonsyndromic deafness and is associated with neuronal dysfunction [64]. However, prior to this review, the specific role of pejvakin in pyroptosis and PF remained unclear.

Molecular mechanisms of pyroptosis

The regulatory mechanisms of pyroptosis are intricate, involving multiple interrelated and overlapping signaling pathways [16]. In molecular terms, dying cells that elicit pyroptosis can be classified into several distinct pathways: the canonical pathway, the non-canonical pathway, and the alternative pathway (Fig. 1).

Canonical pathway

The canonical pyroptotic death, which revolves around caspase-1 and inflammasome activation, is orchestrated through a sequential cascade of two distinct steps [67]. Firstly, PAMPs and DAMPs are recognized by Toll-like receptors (TLRs) in response to both intracellular and extracellular stimuli. These molecular events trigger the activation of the MyD88/NF-κB pathway, initiating the synthesis of pro-IL-1β/18 and transcriptionally promoting the expression of inflammasome genes [36]. The second step revolves around inflammasome assembly and caspase-1 activation [68]. The canonical inflammasome complex comprises an adaptor protein known as the apoptosis-associated speck-like protein (ASC), an inactive pro-caspase-1, and PRRs [37]. Noteworthy, only five specific PRRs have been identified as direct co-inflammasomes that activate caspase-1 via the canonical pathway, including NLR family pyrin domain-containing (NLRP)1, NLRP3, NLRC4, Pyrin, and absent in melanoma 2 (AIM2) [23]. The assembly of inflammasomes, particularly the NLRP3 inflammasome, triggers the hydrolysis of inactive pro-caspase-1 into mature cleaved caspase-1 [69]. Significantly, activated caspase-1 cleaves GSDMD to produce GSDMD-NT and processes pro-IL-1β/18 into IL-1β/18 [70]. Subsequently, GSDMD-NT recognizes and binds to the membrane lipids on the cytoplasmic side of the cell membrane where it oligomerizes to generate cell membrane pores [71]. Transmembrane holes induce potassium (K^+) and water influx, leading to cell swelling, rupture, and subsequent release of IL-1β/18, LDH, and HMGB1 along with other cellular contents, leading to an exacerbated inflammatory response in the host [72].

In particular, the assembly of NLRP3 inflammasome involves three distinct mechanisms. First, mtDNA and the thioredoxin-interacting protein (TXNIP) promote ROS production, which subsequently activates the NLRP3 inflammasome [73]. Second, extracellular triphosphate (ATP) binds to the purinergic P2X7 receptor (P2X7R), triggering NLRP3 activation through potassium efflux [74]. Finally, crystalline or particulate agents induce lysosomal rupture, causing the release of lysosomal cathepsins B and L, which facilitate the assembly of the NLRP3 inflammasome [23].

Non-canonical pathway

The non-canonical pyroptotic death pathway operates primarily depends on the activation of caspase-4/5/11 [17]. These caspases directly interact with lipopolysaccharide (LPS) from gram-negative bacteria via their N-terminal CARD, bypassing the requirement for inflammasome sensors [75]. Subsequently, LPS triggers the activation of caspase-4/5/11, removing the intramolecular inhibition of GSDMD-NT [14]. The liberated GSDMD-NT then binds to cell membrane phospholipids, initiating a series of cascaded events similar to canonical pyroptotic cell death, ultimately facilitating the secretion of cellular content. Significantly, caspase-4/5/11 are unable to

catalyze the conversion of pro-IL-1β/18 into their bioactive forms [76]. Instead, they activate the NLRP3 inflammasome and caspase-1, resulting in the maturation and secretion of IL-1β/IL-18 via the GSDMD holes [77]. Furthermore, activated caspase-11 also splits pannexin-1, promoting the discharge of cellular ATP and inducing pyroptosis through activation of P2X7R, thus amplifying the inflammatory response [78].

Alternative pathway

Caspase-3 and caspase-8 have traditionally been regarded as key markers of apoptosis. However, as our understanding of pyroptosis mechanisms grows, a growing body of research has documented the involvement of apoptosis-associated caspases in the molecular pathways underlying pyroptosis [79]. It is noteworthy that caspase-8 and caspase-9, two apoptosis initiators, can activate caspase-3 [80, 81]. Additionally, in contrast to canonical and non-canonical pathways, caspase-3-mediated pyroptosis does not necessitate the assembly of the inflammasome. Unlike caspase-1/4/5/11, which cleave GSDMD, caspase-3 specifically cleaves GSDME to generate GSDME-NT and form membrane pores that induce cell swelling and lysis [20, 82]. Interestingly, the expression level of GSDME is recognized as a critical determinant in caspase-3-mediated RCD mechanisms. In the presence of adequate levels of GSDME, cells tend to undergo pyroptosis instead of apoptosis in response to intrinsic or extrinsic stimuli [20]. Recently, two independent research groups reported a novel pyroptosis mechanism mediated by caspase-8. In response to Yersinia infection, the effector protein YopJ inhibits the activity of TGF-β-activated kinase-1 (TAK1) or IkappaB kinase (IKK), leading to caspase-8-regulated cleavage of GSDMD [83]. Additionally, Sarhan and colleagues demonstrated that caspase-8 is activated by the concurrent stimulation of LPS and (5Z)-7-Oxozeaenol, a small-molecule inhibitor targeting TAK1 [84]. Subsequently, the activated caspase-8 splits GSDMD to trigger pyroptosis in murine macrophages [84]. Moreover, as previously mentioned, antibiotic chemotherapy agents can also induce caspase-8/GSDMC-modulated pyroptotic cell death in tumor cells [19]. In the granzyme-mediated pathway, CTLs secrete GzmA, which cleaves GSDMB directly at the Lys229/Lys244 site, thereby triggering pyroptosis independently of caspases [48]. Additionally, GzmB derived from CTLs and NK cells directly cleaves GSDME, eliciting pyroptosis and enhancing the antitumor immune response [82]. In a separate pathway involving Streptococcus, pyroptosis is initiated by Streptococcal pyrogenic exotoxin B through the cleavage of GSDMA [24]. These discoveries underscore the significant involvement of granzymes in initiating pyroptosis.

The distinct characteristics of pyroptosis differentiate it from other RCD modalities

Cell death is generally categorized into two types: accidental cell death (ACD) and RCD, differentiated by their occurrence rate and susceptibility to modulation by drugs or genetic factors [85]. The major types of RCD, including apoptosis and non-apoptotic modes (e.g., pyroptosis, necroptosis, ferroptosis, and cuproptosis), each with distinct initiators, effectors, and executors [86] (Table 1). These RCD subroutines exhibit unique characteristics yet share similar features, with significant overlap and intercommunication, as depicted in Fig. 2.

Necroptosis is an inflammatory form of RCD characterized by cytoplasmic vacuolization, organelle swelling, and cytoplasmic membrane rupture [87]. Mechanistically, necroptosis is initiated by death receptors and involves the activation of mixed lineage kinase domain-like protein (MLKL)/pMLKL through the receptor-interacting protein kinase 1 (RIPK1) and RIPK3-regulated phosphorylation signaling pathway [88]. This signaling cascade leads to the formation of MLKL pores, which facilitate the release of cellular contents [89]. In 2012, researchers identified a ferrous ion (Fe^{2+})-dependent RCD form termed ferroptosis, which involves lipid peroxidation, glutathione (GSH) depletion, and mitochondrial dysfunction [90]. Key morphological features of ferroptosis include the loss or reduction of mitochondrial cristae, condensation of the mitochondrial membrane, and disruption of cell membrane integrity, ultimately leading to cell lysis [91]. Cuproptosis is initiated by excessive mitochondrial Cu^{2+} accumulation, which induces the aggregation of lipoylated dihydrolipoamide S-acetyltransferase (DLAT), a protein associated with the mitochondrial tricarboxylic acid (TCA) cycle. These molecular events destabilize Fe-S cluster proteins, culminating in proteotoxic stress and cell death [92].

Like necroptosis, pyroptosis is a pro-inflammatory RCD mechanism. Of note, pyroptosis exhibits distinct characteristics in comparison to other RCD mechanisms. Firstly, in the initial phase of pyroptosis, the intact nuclei of pyroptotic cells undergo chromatin condensation and DNA fragmentation, distinguishing it from apoptosis [93]. Additionally, apoptotic cells exhibit preserved membrane integrity compared to pyroptotic cells [94]. Cellular uptake of membrane-penetrating dyes, such as ethidium bromide, serves as a reliable approach for assessing the occurrence of pyroptosis [95]. Secondly, in necroptosis, ferroptosis, and cuproptosis, abnormal plasma membrane permeability leads to cell swelling and osmotic lysis [96]. Unlike pyroptosis, these processes do not rely on inflammasome activation or the generation of gasdermin-dependent cell membrane pores [97]. Instead, they are regulated by different effectors, such as MLKL in

Table 1 Comparison of characteristics of apoptosis, necroptosis, ferroptosis, cuproptosis, and pyroptosis

Type of cell death	Inducer	Cellular morphological features	Key biochemical pathway components	Initiator caspase	Core characteristic (s)	Major executor	Inflammation features	Ref.
Apoptosis	TNF-α, FasL, TRAIL, Hypoxia, Irradiation, Heat shock	Bubbling plasma membrane, shrunkern cells, chromatin aggreegation and condensation	Apaf-1, caspase-3/7/8/9, cytochrome c, Bid/tBid, BAX/BAK, BCL-2, and NF-κb	Caspase-3/7/8/9	Apoptotic body	Caspases	non-inflammatory	[18, 86]
Pyroptosis	DAMPs, PAMPs, Microbial infection, granzymes	Cell swelling, membrane pores formation, membrane rupture, plasma membrane blebbing, moderately condensed chromatin	Inflammasomes, caspase-1/3/4/5/8/11, gasdermins, IL-1β, and IL-18	Caspase-1/3/4/5/8/11	Inflammasome	Gasdermins	Inflammatory cell death	[14, 15, 17, 21]
Necroptosis	TNF-α, TRAIL, Fas ligand, Microbial infection	Cytoplasmic swelling, pore formation on cells membranes, loss of plasma membrane integrity, swelling of cytoplasmic organelles, and moderate chromatin condensation.	RIPK1, RIPK3, TRADD, NMEO, caspase-8, and MLKL	Caspase-8/10	Necrosome	RIPK1, RIPK3, MLKL	Inflammatory cell death	[87–89]
Ferroptosis	Fe^{3+}, cystine, lipid peroxidation	Cells swelling, pore formation on cells membranes, smaller mitochondria with decreased cristae, elevated mitochondrial membrane densities, and accumulation of lipid peroxides in plasma membranes	Fe^{2+}, GPX4, ROS, PUFAs, ACSL4, LPCAT3, ALOXs, SLC40A1, TF-TFRC,	No	Iron accumulation and lipid peroxidation	GPX4	Inflammatory cell death	[90, 91]
Cuproptosis	Cu^{2+}	Mitochondrial shrinkage, mitochondrial membrane rupture, reduction in the mitochondrial crest and mitochondrial membrane lysis	Cu^{+}/Cu^{2+}, FDX1, GPX4, SLC31A1, LIAS, ROS, ATP7A/B, GSH	No	DLAT aggregation and loss of Fe-S cluster	FDX1	Undetermined	[92]

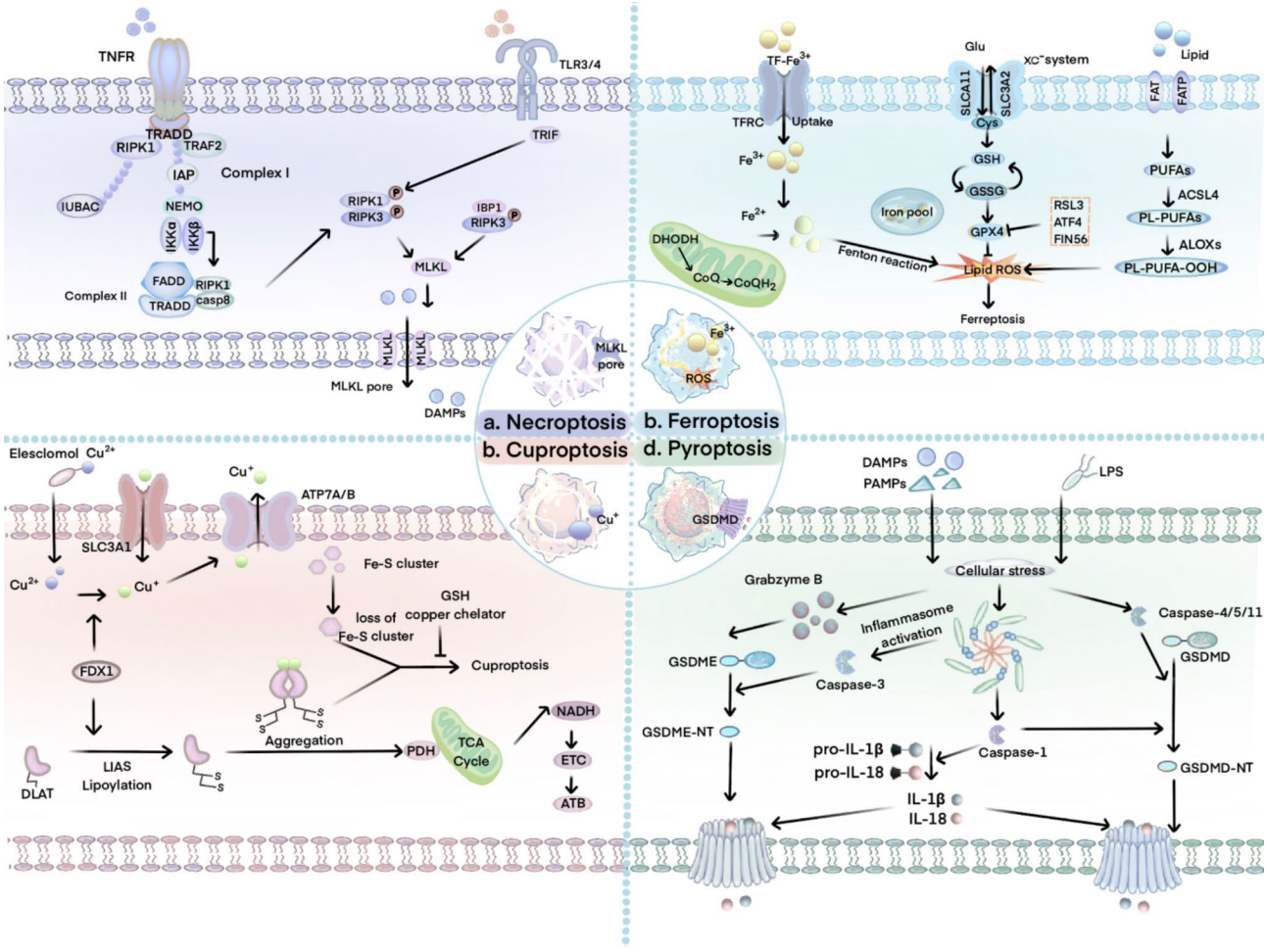

Fig. 2 Pathways controlling necroptosis, ferroptosis, cuproptosis, and pyroptosis. (**a**) Necroptosis is triggered by death receptors, such as FAS and tumor necrosis factor receptor 1, and is mediated by RIP1, RIP3, and MLKL, resulting in MLKL pore formation. This process typically occurs when the caspase-8-dependent extrinsic apoptosis pathway is inactive. (**b**) Ferroptosis is an iron-dependent form of RCD that is primarily driven by lipid peroxidation. It is characterized by intracellular iron overload and the generation of ROS. The ACSL4/LPCAT3/ALOXs pathway drives ferroptosis through lipid peroxidation and PLOOH formation, aided by RAB7A-dependent lipophagy. Specifically, GPX4 catalyzes the reduction of glutathione, inhibiting lipid peroxidation and ferroptosis. (**c**) The accumulation of free copper ions can induce cuproptosis. Copper ionophores like elesclomol transport extracellular copper into cells, where it binds to lipoylated mitochondrial enzymes in the TCA cycle, such as DLAT, causing aggregation. The FDX1/LIAS axis reduces Cu^{2+} to Cu^{+}, promoting protein aggregation and Fe-S cluster loss, leading to proteotoxic stress and cell death. (**d**) The primary pyroptosis model includes both GSDMD-dependent and independent pathways. Cytoplasmic sensor proteins, such as NLRP1, NLRP3, NLRP4, AIM2, and Pyrin, are activated by PAMPs or DAMPs and recruit the adaptor ASC, leading to caspase activation. Activated caspases, including caspase-1/4/5/11, cleave GSDMD to generate GSDMD-NT, while caspase-3 cleaves GSDME to produce GSDME-NT. These events culminate in pore formation, cell lysis, and the release of cellular contents

necroptosis, polyunsaturated fatty acids (PUFAs) in ferroptosis, and Fe-S cluster proteins in cuproptosis [86].

Molecular insights into PF pathophysiology

The pathogenesis of PF, including IPF, cystic fibrosis lung disease, smoking and silicosis-induced PF, is driven by three primary factors: persistent chronic inflammatory response, senescence, and genetic susceptibility [10]. The initial stages of PF are characterized by the presence of numerous inflammatory factors associated with innate and adaptive immune responses [98]. Typically, this pathological process consists of three stages: inflammation, proliferation, and remodeling. The initial event is believed to involve injury to the AECs, leading to a robust inflammatory reaction that recruits various inflammatory cells, including lymphocytes, macrophages, basophils, eosinophils, and mast cells [99]. Of note, in response to cellular stress, the aberrant activation and over-proliferation of type II alveolar epithelial cells (AEC-II) can result in prolonged inflammatory responses and the onset of fibrotic pathologies. Consequently, a cascade of pro-fibrotic factors triggers the transition of AECs into a mesenchymal phenotype through the process of epithelial-mesenchymal transition (EMT), ultimately culminating in destruction of the basement membrane [100]. Alveolar macrophages, as the predominant immune

cells in pulmonary tissues, initiate pyroptosis-associated inflammatory signaling cascades and significantly contribute to the airway remodeling process [101]. Furthermore, the intricate interplay between macrophages and the microenvironment regulates tissue regeneration, characterized by unique surface markers that promote either pro-regenerative or profibrotic outcomes [57]. Importantly, both M1 and M2 macrophages play crucial roles in the early inflammatory stage of PF [102]. Initially, an excessive polarization of macrophages towards the M1 phenotype leads to AECs demise and the release of pro-inflammatory factors, triggering the early inflammatory phase [103]. Subsequently, pulmonary-infiltrating M2 macrophages secrete a multitude of chemokines, matrix metalloproteases, and pro-fibrotic soluble mediators, which exacerbate the progression of PF during the remodeling phase [100]. These molecular events trigger the proliferation and differentiation of fibroblasts into myofibroblasts, a distinct subtype characterized by high matrix remodeling activity and capability to produce ECM components (e.g., I, III, and IV collagen proteins, α-SMA, laminin (LN) type, and MMPs), leading to the thickening and sclerosis of lung tissue, ultimately contributing to PF [104]. Collectively, addressing excessive inflammation is of the utmost importance in the prevention of PF.

Functional role of pyroptosis in pulmonary inflammation and fibrosis

Pyroptosis is regarded as a crucial immune defense mechanism of the host. Recent studies have shed light on the pivotal role of pyroptosis in the progression of pulmonary inflammation and fibrosis (Fig. 3). Notably, the association between pyroptosis and PF varies depending on histology, genetic background, and the complexity of the inflammatory microenvironment under different conditions [105]. Evidence suggests that levels of caspase-1 and IL-1β are significantly elevated in the bronchoalveolar lavage fluid (BALF) of PF mice [106]. Additionally, the upregulation of AIM2 expression has been identified in the alveolar macrophages of PF patients and in a mouse model of PF induced by bleomycin [107]. Furthermore, it has been reported that dysregulated expression of NLRP3 in alveolar macrophages is associated with the development of PF [108]. In models of bleomycin-induced PF, mice deficient in NLRP3, ASC, and caspase-1 exhibited reduced IL-1β secretion, leading to mitigation of pulmonary inflammation and fibrosis [28, 108]. Therefore, pharmacological agents that inhibit inflammasome activation hold the potential to improve the treatment of PF by preventing pyroptosis. According to recent research by Song et al., it was found that inhibition of GSDMD-mediated pyroptosis significantly mitigates the advancement of pulmonary inflammation and fibrosis induced by silica exposure [56]. Intriguingly, GSDMD-deficient mice exhibited dramatically alleviated silicosis phenotypes [56]. Consistent with the aforementioned findings, additional research has demonstrated that GSDMD knockdown inhibits silica-induced macrophage pyroptosis and mitigates the upregulation of fibrotic markers in fibroblasts, highlighting the crucial role of GSDMD in the pathogenesis of PF [57]. In recent years, multiple studies have implicated that GSDME-mediated pyroptosis in the progression of fibrotic diseases such as renal fibrosis and peritoneal fibrosis; however, the specific role of GSDME in PF has yet to be determined [58, 109]. Moreover, it remains unclear whether other gasdermin family proteins such as GSDMA, GSDMB, GSDMC, GSDME and DFNB59 are also involved in this devastating disease.

Potential anti-fibrotic therapeutic drugs that target pyroptosis

In our previous discussion, we detailed the molecular mechanisms of pyroptosis and the signaling pathways involved in its role in pulmonary inflammation and fibrosis, emphasizing potential therapeutic strategies that target the pyroptotic cascade. Specifically, therapies can be designed to inhibit the assembly of inflammasomes, the activation of caspase-1, the cleavage of GSDMD, the secretion of IL-1β/18, and the upstream signaling pathways (Table 2).

Inflammasome-related therapy

Under normal physiological conditions, the NLRP3 inflammasome plays a critical role in maintaining homeostasis and metabolic equilibrium [110]. Nevertheless, overexpression of NLRP3 can trigger pyroptotic cell death. Therefore, inhibition of NLRP3 activation presents a promising therapeutic strategy for the treatment of pulmonary inflammation and fibrosis. Lycorine, an alkaloid isolated from the *Amaryllidaceae* family, effectively mitigates bleomycin-induced pulmonary inflammation and fibrosis by suppressing the activation of the NLRP3 inflammasome and pyroptosis in macrophages through targeting the PYD domain of ASC [29]. These findings indicate that Lycorine could be a promising therapeutic agent for pulmonary inflammation and fibrosis [29]. Iguratimod is a novel therapeutic agent for the management of connective tissue disease (CTD). Clinical studies have established its efficacy in enhancing pulmonary function and its promising role in the treatment of PF [111]. Nonetheless, the precise mechanisms underlying its action remain to be elucidated. Recent research has demonstrated that iguratimod markedly mitigates bleomycin-induced PF through the suppression of NLRP3 inflammasome activation, reduction of ROS production, and inhibition of the EMT process [112]. Elamipretide, also known as SS-31, is an innovative

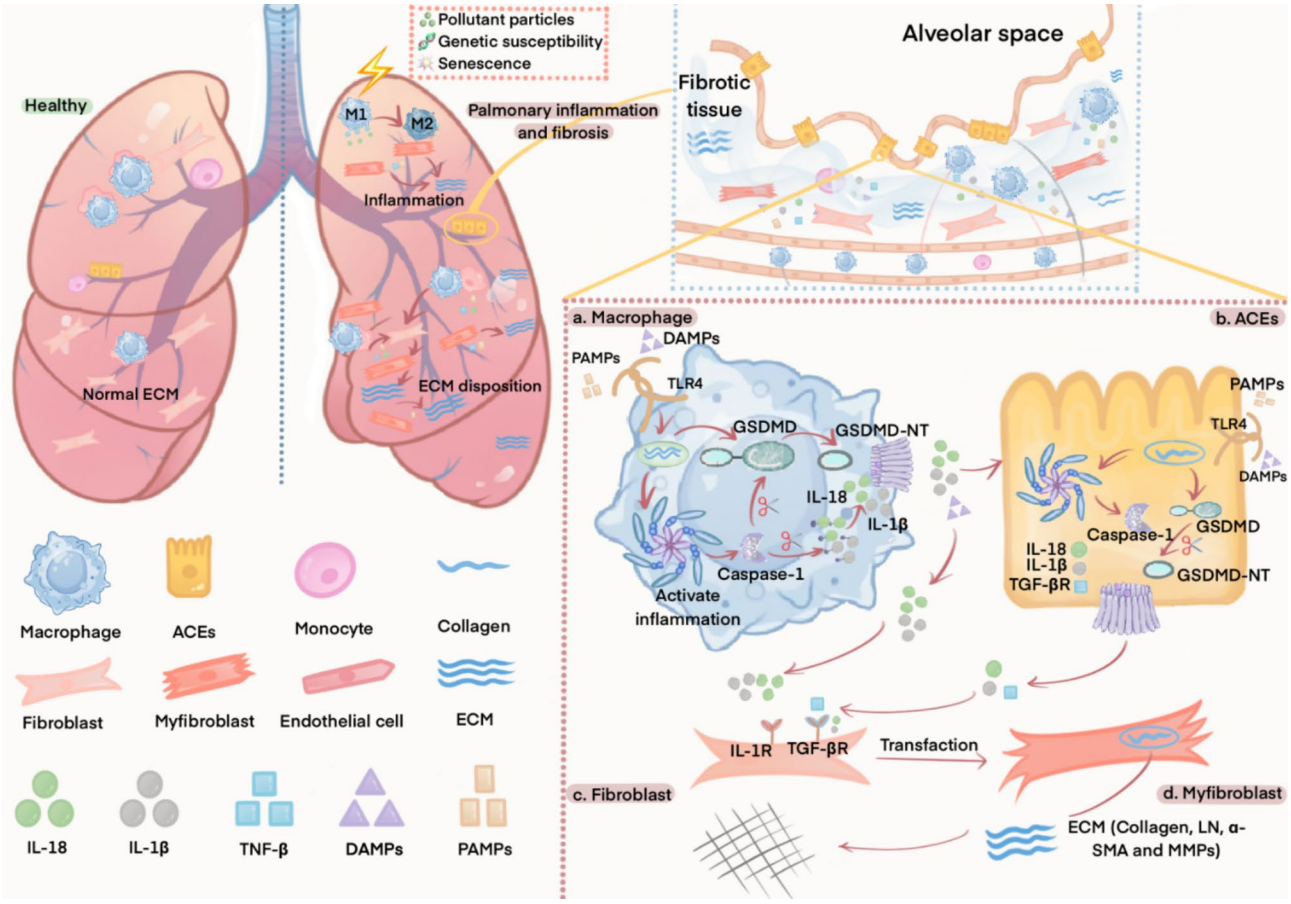

Fig. 3 Schematic illustration of the regulatory role of pyroptosis in pulmonary inflammation and fibrosis. Excessive epithelial damage induced by inhaled pollutants, genetic factors, senescence, and other exogenous or endogenous danger signals triggers pulmonary inflammation and fibrosis. The initial injury to AECs prompts a robust inflammatory response, recruiting inflammatory cells such as macrophages, monocytes, and lymphocytes. Stimulation of macrophages by DAMPs or PAMPs activates PRRs, triggering inflammasome assembly and the cleavage of pro-caspase-1. Activated caspase-1 then cleaves GSDMD to release GSDMD-NT and processes pro-IL-1β/18 into their mature forms, which are released through GSDMD pores. These molecular events promote the excessive polarization of M1 macrophages to M2 macrophages, leading to AECs pyroptosis and the release of proinflammatory factors and TGF-β. Simultaneously, fibroblasts upregulate the expression of TGF-β receptor. In response to proinflammatory factors and TGF-β stimulation, fibroblasts undergo trans-differentiation into myofibroblasts, a specialized subtype characterized by high matrix remodeling activity and the ability to generate ECM components such as collagen proteins, α-SMA, LN, and MMPs. This pathological process leads to thickening and sclerosis of lung tissue, ultimately resulting in PF

mitochondria-targeted peptide that scavenges mtROS and removes damaged mtDNA [113]. Nie et al. demonstrated that SS-31 provides protection against PF and inflammation by suppressing Nrf2-mediated NLRP3 inflammasome activation in macrophages, leading to reduced expression of IL-1β and IL-18 [113]. Betanin exhibits various pharmacological properties, such as anti-diabetic, antioxidant, and anti-inflammatory actions [114]. Abd Elrazik and colleagues reported that betanin plays a protective role against bleomycin-induced PF by modulating the NLRP3/IL-1β/TGF-β1 pathway, which governs the EMT process [114]. It has been revealed that pemafibrate, a selective peroxisome proliferator-activated receptor alpha (PPARalpha) agonist, can inhibit the activation of the NLRP3/caspase-1 axis and TGF-β1-induced myofibroblast differentiation, which further decreases ECM deposition [115]. Mirtazapine, an atypical antidepressant drug, is classified as a tetracyclic antidepressant [116]. Intriguingly, a recent study in 2023 demonstrated the anti-inflammatory properties of mirtazapine, indicating its ability to exert an anti-fibrotic effect against PF by inhibiting NLPR3 inflammasome and fibrosis-related mediators [117]. MCC950, a highly selective small-molecule inhibitor of the NLRP3 inflammasome, has restricted clinical use due to its pharmacokinetic and toxicokinetic profile [118]. Mechanistically, MCC950 interacts specifically with the NACHT domain of NLRP3, thwarting ATP hydrolysis and inflammasome assembly [119]. A recent study has demonstrated that MCC950 alleviates pulmonary inflammation and fibrosis induced by silica nanoparticles [105]. This therapeutic effect is achieved by inhibiting NLRP3 expression and

Table 2 The summary of potential therapeutic drugs regulating pyroptosis for PF

Drug name	Models	Targeting marker	Potential mechanism	Ref
Lycorine	BLM-induced PF mice, LPS/Nigericin stimulated BMDMs	NLRP3	Disturbs the interaction of NLRP3 with ASC by targeting the PYD domain on Leu9, Leu50, and Thr53	[29]
Iguratimod	BLM-induced PF mice, TGF-induced A549 EMT cell model	NLRP3	Suppresses NLRP3 inflammasome activation, reduces ROS production, and inhibits the EMT process	[112]
Elamipretide	BLM-induced PF mice, $Nrf2^{-/-}$ mice and macrophages	NLRP3, Nrf2	Blocks the Nrf2-mediated NLRP3 inflammasome activation in macrophages	[113]
Betanin	BLM-induced PF rats	NLRP3	Modulating the NLRP3/IL-1β/TGF-β1 pathway and governs the EMT process	[114]
Pemafibrate	BLM-induced PF rats, TGF-β1 stimulated lung fibroblasts	PPARα	A selective PPARα agonist, partly inhibits the activation of the NLRP3/caspase-1 axis and TGF-β1-induced myofibroblast differentiation	[115]
Mirtazapine	BLM-induced PF rats	NLRP3	Inhibiting NLRP3 inflammasome activation can reduce the expression of fibrosis-related mediators	[117]
MCC950	Silica nanoparticle-induced PF mice, silica-induced pyroptotic macrophages and fibroblasts	NLRP3	inhibiting NLRP3 expression and simultaneously activating relaxin and osteoclast differentiation signaling pathways to reprogram fibroblasts	[105]
VX-765	Silica-induced PF mice, silica-induced pyroptotic alveolar macrophages	Caspase-1	Covalently modifies catalytic cysteine residues in the active site of caspase-1, downregulates pro-inflammatory and pro-fibrotic cytokines	[123]
Ac-YVAD-CMK	BLM-induced PF mice, BLM stimulated HPMECs	Caspase-1	Alleviates BLM-induced pulmonary fibrosis by directly targeting caspase-1	[124]
Disulfiram	Crystalline silica particles-induced PF mice, silica-induced pyroptotic alveolar macrophages	GSDMD	Directly targets Cys191/Cys192 in GSDMD-NT, inhibits silica-induced alveolar macrophage pyroptosis, alleviates fibrotic pathological damage in the lungs of silicotic mice	[28]
Necrosulfonamide	Pulmonary IRI rat model	GSDMD, MLKL	Blocking the oligomerization of p30-GSDMD and preventing the pyroptotic pores formation	[130]
Canakinumab	CVB3 myocarditis mouse model	IL-1β	IgGκ monoclonal antibody targeting IL-1β, downregulates pro-inflammatory and pro-fibrotic cytokines	[136]
Anakinra	Cystic fibrosis mouse models, Scnn1b-transgenic mice with cystic fibrosis and lung injury	IL-1β	Selective recombinant antagonist of the IL-1β receptor, obstructing the IL-1β-mediated pathway	[141–143]
Liproxstatin-1	BLM-induced PF mice, BLM stimulated A549	ROS	Targeting ROS and modulating the ROS/p53/α-SMA pathway	[146]
Thalidomide	BLM-induced PF mice, TGF-β1 stimulated lung fibroblasts	ROS	Inhibits the progression of PF by exerting anti-inflammatory effects through the inhibition of ROS-related oxidative stress	[149, 150]
A438079	α-sarcoglycan knockout mice, LPS-stimulated macrophages and LX-2 cells	P2X7R	P2X7R antagonist that inhibits potassium (K^+) efflux, blocking the P2X7/NLRP3 inflammasome axis and inhibiting fibrogenesis	[153, 154]
Trikafta	Cystic fibrosis patients	P2X7R	Inhibits ATP/P2X7R-induced inflammasome activation and exhibits anti- inflammatory effects	[155]

simultaneously activating relaxin and osteoclast differentiation signaling pathways, which reprogram fibroblasts [105]. Consequently, given their remarkable efficacy in animal models, it is essential to pursue clinical trials of inflammasome-targeted therapies to evaluate their effectiveness in treating PF in humans.

Caspase-1-related therapy

Caspase-1, a significant proteolytic enzyme, plays a crucial role in the pathogenesis of PF in animal models, driving the exploration of caspase-1 inhibitors as promising therapeutic agents. To date, several caspase-1 inhibitors have been identified, including Belnacasan (VX-765) and Ac-YVAD-CMK, which have garnered significant attention [120, 121]. VX-765, a selective small molecule, inhibits caspase-1 activation by covalently modifying the catalytic site of caspase-1, thereby hindering caspase-1-dependent pyroptosis [122]. A recent study demonstrated that VX-765 mitigates silica-induced lung inflammation and fibrosis by modulating the pyroptosis of alveolar macrophages in mice [123]. Mechanistically, VX-765 targets caspase-1 specifically and downregulates pro-inflammatory and pro-fibrotic cytokines, thereby alleviating systemic and local inflammatory responses caused by silica [123]. Similarly, as a specific caspase-1 inhibitor, intraperitoneally administered Ac-YVAD-CMK significantly alleviates bleomycin-induced PF by directly targeting caspase-1 [124]. Moreover, Ac-YVAD-CMK

inhibits the NLRP3 inflammasome activation and EMT process by suppressing the focal adhesion kinase (FAK) pathway [124]. Overall, the therapeutic targeting of caspase-1 in PF is under-researched, necessitating further exploration.

Gasdermin-related therapy

As the primary executor of pyroptosis, GSDMD targeted interventions have garnered significant interest for the treatment of diverse diseases. Disulfiram (DSF), an FDA-approved medication for treating alcohol dependency, has recently been demonstrated to inhibit pyroptosis and the inflammatory cascade within cells [125]. Mechanistically, DSF directly targets Cys191/Cys192 in GSDMD-NT, binding to acidic phospholipids within the inner leaflet of the cellular plasma membrane, thereby blocking GSDMD pores formation [125]. Silva and colleagues reported that DSF alleviate excessive neutrophil extracellular traps (NETs)-based injury associated with sepsis, indicating that disulfiram have potential anti-inflammatory effects and improve sepsis therapeutic outcomes [126]. Another study demonstrated that DSF effectively inhibited LPS-induced lung inflammation in an acute lung injury (ALI) mouse model [127]. However, the absence of Bhlhe40 suppressed GSDMD-mediated pyroptosis and subsequent ALI by suppressing both canonical and non-canonical inflammatory signaling pathways [127]. DSF also exhibits anti-fibrosis effects. Recent research indicates that DSF could inhibit silica-induced alveolar macrophage pyroptosis, alleviate fibrotic pathological damage in the lungs of silicotic mice by targeting GSDMD [28]. Necrosulfonamide was originally identified as an inhibitor of necroptosis through its direct binding to MLKL [128]. However, a more recent study revealed that necrosulfonamide can also directly interact with GSDMD, thereby blocking the oligomerization of p30-GSDMD and preventing the pyroptotic pores formation [129]. In a rat model of pulmonary ischemia/reperfusion injury (IRI), the administration of necrosulfonamide markedly enhanced lung physiological functions [130]. However, further research is needed to determine the efficacy of this inhibitor in treating PF.

IL-1β-related therapy

As previously mentioned, IL-1β is a critical effector molecule in the pyroptotic pathway and contributes to lung damage, suggesting its potential as a therapeutic target for PF [131]. Canakinumab, a human monoclonal antibody, exhibits high affinity and specificity for human IL-1β by inhibiting its interaction with the IL-1 receptor (IL-1R) [132]. Canakinumab has been used in treating autoinflammatory disorders, atherosclerosis, and chronic obstructive pulmonary disease [133–135]. Studies also suggest that canakinumab may inhibit the IL-1β signaling pathway to prevent the progression of chronic viral myocarditis by reducing inflammation, interstitial fibrosis, and adverse cardiac remodeling, indicating potential anti-fibrotic effects [136]. However, its therapeutic effects on PF remain unknown, and further research in this area is eagerly awaited. Anakinra, a selective IL-1β receptor antagonist, has shown clinically significant benefits along with an outstanding safety profile [137]. Anakinra has proved effective for various IL-1β-driven inflammatory pathologies such as rheumatoid arthritis, pericarditis, and hemodialysis-induced inflammation [138–140]. Notably, anakinra also exhibits anti-fibrotic properties. Fritzsching et al. recently demonstrated that anakinra treatment could attenuate hypoxia-induced epithelial necrosis, thereby diminishing neutrophilic inflammation through IL-1 receptor signaling pathways in Scnn1b-transgenic mice with cystic fibrosis and lung disease [141]. Interestingly, Puccetti et al. discovered that pulmonary delivery of an inhalable form of anakinra notably improved and prolonged therapeutic efficacy in cystic fibrosis mouse models by obstructing the IL-1β-mediated pathway [142]. Additionally, a case series reports that anakinra shows promising efficacy and safety in treating COVID-19-associated PF [143]. However, further high-quality research is needed to clarify its potential clinical efficacy in treating PF.

Suppression of upstream signals

Current evidence indicates that heightened bronchoalveolar sensitivity to ROS and ROS-induced DNA damage contribute to pulmonary inflammation and fibrosis in an ataxia-telangiectasia-deficient mouse model [144]. Considering the critical biological role of ROS in pyroptosis, targeting ROS-associated redox equilibrium could be a promising therapeutic approach [144]. Liproxstatin-1, a potent inhibitor of lipid autoxidation, exerts a strong inhibitory effect on ROS activity [145]. It plays a protective role in mice with bleomycin-induced PF by targeting the ROS/p53/α-SMA pathway [146]. Thalidomide was previously clinically banned due to its teratogenic effects on the fetus [147]. However, subsequent studies have revealed that this compound exhibits potent anti-inflammatory properties [148]. Recent research has suggested that thalidomide inhibits the progression of PF by exerting anti-inflammatory effects through the inhibition of ROS-related oxidative stress [149, 150]. P2X7R is a membrane protein that can be stimulated by extracellular ATP and functions as an upstream molecule of the NLRP3 inflammasome [74]. P2X7R activation is associated with various physiological processes, notably inflammatory responses and the development of fibrosis [151]. The blockade of P2X7R potentially mitigates fibrosis via multiple mechanisms, such as reducing inflammatory or fibrotic markers and modulating the recruitment of

immune cells to regulate inflammation [152]. A438079, a potent and selective P2X7 antagonist, has been demonstrated to regulate collagen expression and improve muscle force by reducing the extent of muscle fibrosis and local inflammation in α-sarcoglycan null mice [153]. A separate study demonstrated that the administration of A438079 can block the P2X7/NLRP3 inflammasome axis, thereby inhibiting stellate cell activation and subsequent liver fibrogenesis [154]. The triple-drug combination therapy, Trikafta (elexacaftor/tezacaftor/ivacaftor), has received approval for the treatment of cystic fibrosis. Notably, it has been revealed that Trikafta also inhibits ATP/P2X7R-induced inflammasome activation and exhibits anti-inflammatory effects [155]. Despite P2X7R inhibitors have shown promise in treating fibrotic diseases, the research regarding their effectiveness in addressing pulmonary inflammation and fibrosis remains inadequate.

Conclusion and perspective

PF is a chronic inflammatory lung disease, and recent studies have shed light on the involvement of pyroptosis in its pathogenesis. Growing evidence underscoring the involvement of inflammasome pathways in PF indicates that gasdermins and pyroptosis are also implicated to some extent. Mechanistically, the excessive and persistent activation of the inflammasome and pyroptosis in ACEs and alveolar macrophages lead to a pronounced inflammatory response. This, in turn, accelerates the transformation of fibroblasts into myofibroblasts, eventually culminating in PF. In this review, we systematically summarize current discoveries regarding the intricate molecular mechanisms of pyroptosis and examine its crosstalk interactions with relevant signaling pathways. Furthermore, we highlighted potential drugs to impede the pyroptotic pathway for anti-PF treatment. Indeed, an in-depth comprehension of the role of pyroptosis in PF provides significant insights for potential therapeutic strategies.

Despite notable advancements, pyroptosis-mediated therapy still encounters several challenges. Firstly, compared to cancer and other diseases, research on pyroptosis in PF is in its early stages. Therapies targeting gasdermins are limited and warrant further exploration in the future. Secondly, it is imperative to identify the upstream regulators of pyroptosis owing to the intricate interplay among other cell death pathways and the diverse gasdermin activation mechanisms that go beyond the workings of canonical or non-canonical pyroptotic pathways. Given that GzmA, GzmB, and streptococcus cysteine protease SpeB could cleave gasdermins, it is no longer appropriate to simply assume that inflammasome activation equates with pyroptosis. Moreover, the regulatory roles of mitochondria and endoplasmic reticulum in pyroptosis warrant further investigation. Furthermore, the precise roles of the mitochondria and endoplasmic reticulum in the regulation of pyroptosis remain inadequately characterized in the current literature. Thirdly, utilizing inhibition of pyroptosis as a therapeutic response could potentially lead to adverse effects considering the crucial role of this cell death mechanism involved in normal physiological functions. Inappropriately orchestrated induction of pyroptosis may lead to detrimental effects on normal tissue adjacent to fibrotic tissue. Future research should prioritize the development of strategies to overcome these limitations and devise inhibitors specifically targeted at fibrotic tissues to mitigate potential side effects. Finally, observations gathered from cellular and animal studies need validation in clinical trials to confirm the effectiveness of targeting pyroptosis or its upstream regulators in PF patients. Additionally, the long-term effects, safety profiles, drug interactions, and patient-specific applications of pyroptosis inhibitors remain unknown, warranting further investigation.

In summary, it is evident that the underlying mechanisms of pyroptosis implicated in the pathological process of pulmonary inflammation and fibrosis are yet to be completely unraveled. Further research employing cell-specific transgenic and conditional knockout animal models exhibiting pyroptosis deficiencies, such as $NLRP3^{-/-}$ and $GSDMD^{-/-}$ mice, is of significant interest to precisely address this question. Additionally, more high-quality clinical trials are needed to establish the pharmacokinetics and clinical efficacy of pyroptosis inhibitors in treating pulmonary fibrosis. In the near future, it is recommended that medical organizations conduct clinical trials in which patients receive approved pyroptosis-regulating drugs in combination with antifibrotic agents such as pirfenidone and nintedanib. Future research could also explore the use of nanomaterials, photodynamic therapy, and antibody-drug conjugates (ADCs) to enhance the targeting of pyroptosis inhibitors, thereby reducing potential side effects. We believe that studies focusing on pyroptosis are poised to inaugurate new vistas for the management of PF.

Author contributions

Conceptualization, Yixiang Hu; Original Draft Preparation, Ya Liu and Danxia Wang; Visualization, figures, and tables, Xiang Liu, Haibin Yuan, and Dan Liu; Supervision, Yixiang Hu and Shipeng Ning.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. King TE Jr., Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378(9807):1949–61.
2. Duckworth A, Gibbons MA, Allen RJ, Almond H, Beaumont RN, Wood AR, et al. Telomere length and risk of idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease: a mendelian randomisation study. Lancet Respir Med. 2021;9(3):285–94.
3. Rajan SK, Cottin V, Dhar R, Danoff S, Flaherty KR, Brown KK, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J. 2023;61(3):2103187.
4. O'Reilly S. Pulmonary fibrosis in COVID-19: mechanisms, consequences and targets. QJM. 2023;116(9):750–4.
5. Sgalla G, Kulkarni T, Antin-Ozerkis D, Thannickal VJ, Richeldi L. Update in Pulmonary Fibrosis 2018. Am J Respir Crit Care Med. 2019;200(3):292–300.
6. Ghazipura M, Mammen MJ, Bissell BD, Macrea M, Herman DD, Hon SM, et al. Pirfenidone in Progressive Pulmonary Fibrosis: a systematic review and Meta-analysis. Ann Am Thorac Soc. 2022;19(6):1030–9.
7. Vancheri C, Kreuter M, Richeldi L, Ryerson CJ, Valeyre D, Grutters JC, et al. Nintedanib with add-on Pirfenidone in Idiopathic Pulmonary Fibrosis. Results of the INJOURNEY Trial. Am J Respir Crit Care Med. 2018;197(3):356–63.
8. Koudstaal T, Funke-Chambour M, Kreuter M, Molyneaux PL, Wijsenbeek MS. Pulmonary fibrosis: from pathogenesis to clinical decision-making. Trends Mol Med. 2023;29(12):1076–87.
9. Shenderov K, Collins SL, Powell JD, Horton MR. Immune dysregulation as a driver of idiopathic pulmonary fibrosis. J Clin Invest. 2021;131(2):e143226.
10. Wan Q, Zhang X, Zhou D, Xie R, Cai Y, Zhang K, et al. Inhaled nano-based therapeutics for pulmonary fibrosis: recent advances and future prospects. J Nanobiotechnol. 2023;21(1):215.
11. Noble PW, Barkauskas CE, Jiang D. Pulmonary fibrosis: patterns and perpetrators. J Clin Invest. 2012;122(8):2756–62.
12. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung diseases. N Engl J Med. 2020;383(10):958–68.
13. Tanner L, Single AB, Bhongir RKV, Heusel M, Mohanty T, Karlsson CAQ, et al. Small-molecule-mediated OGG1 inhibition attenuates pulmonary inflammation and lung fibrosis in a murine lung fibrosis model. Nat Commun. 2023;14(1):643.
14. He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, et al. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Res. 2015;25(12):1285–98.
15. Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. Trends Pharmacol Sci. 2022;43(8):653–68.
16. Elias EE, Lyons B, Muruve DA. Gasdermins and pyroptosis in the kidney. Nat Rev Nephrol. 2023;19(5):337–50.
17. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature. 2015;526(7575):666–71.
18. Fritsch M, Günther SD, Schwarzer R, Albert MC, Schorn F, Werthenbach JP, et al. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. Nature. 2019;575(7784):683–7.
19. Zhang JY, Zhou B, Sun RY, Ai YL, Cheng K, Li FN, et al. The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. Cell Res. 2021;31(9):980–97.
20. Wang Y, Gao W, Shi X, Ding J, Liu W, He H, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. Nature. 2017;547(7661):99–103.
21. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 2015;526(7575):660–5.
22. LaRock DL, Johnson AF, Wilde S, Sands JS, Monteiro MP, LaRock CN. Group A Streptococcus induces GSDMA-dependent pyroptosis in keratinocytes. Nature. 2022;605(7910):527–31.
23. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther. 2021;6(1):128.
24. Deng W, Bai Y, Deng F, Pan Y, Mei S, Zheng Z, et al. Streptococcal pyrogenic exotoxin B cleaves GSDMA and triggers pyroptosis. Nature. 2022;602(7897):496–502.
25. Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. Cell Mol Immunol. 2021;18(9):2114–27.
26. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol. 2019;19(8):477–89.
27. Miao R, Jiang C, Chang WY, Zhang H, An J, Ho F, et al. Gasdermin D permeabilization of mitochondrial inner and outer membranes accelerates and enhances pyroptosis. Immunity. 2023;56(11):2523–e418.
28. Wei Y, You Y, Zhang J, Ban J, Min H, Li C, et al. Crystalline silica-induced macrophage pyroptosis interacting with mitophagy contributes to pulmonary fibrosis via modulating mitochondria homeostasis. J Hazard Mater. 2023;454:131562.
29. Liang Q, Cai W, Zhao Y, Xu H, Tang H, Chen D, et al. Lycorine ameliorates bleomycin-induced pulmonary fibrosis via inhibiting NLRP3 inflammasome activation and pyroptosis. Pharmacol Res. 2020;158:104884.
30. Zychlinsky A, Prevost MC, Sansonetti PJ. Shigella flexneri induces apoptosis in infected macrophages. Nature. 1992;358(6382):167–9.
31. Brennan MA, Cookson BT. Salmonella induces macrophage death by caspase-1-dependent necrosis. Mol Microbiol. 2000;38(1):31–40.
32. Wei Y, Lan B, Zheng T, Yang L, Zhang X, Cheng L, et al. GSDME-mediated pyroptosis promotes the progression and associated inflammation of atherosclerosis. Nat Commun. 2023;14(1):929.
33. Orzalli MH, Prochera A, Payne L, Smith A, Garlick JA, Kagan JC. Virus-mediated inactivation of anti-apoptotic Bcl-2 family members promotes gasdermin-E-dependent pyroptosis in barrier epithelial cells. Immunity. 2021;54(7):1447–e625.
34. Wan X, Li J, Wang Y, Yu X, He X, Shi J, et al. H7N9 virus infection triggers lethal cytokine storm by activating gasdermin E-mediated pyroptosis of lung alveolar epithelial cells. Natl Sci Rev. 2022;9(1):nwab137.
35. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nat Rev Microbiol. 2009;7(2):99–109.
36. Loveless R, Bloomquist R, Teng Y. Pyroptosis at the forefront of anticancer immunity. J Exp Clin Cancer Res. 2021;40(1):264.
37. Kovacs SB, Miao EA, Gasdermins. Effectors of Pyroptosis. Trends Cell Biol. 2017;27(9):673–84.
38. Liu X, Xia S, Zhang Z, Wu H, Lieberman J. Channelling inflammation: gasdermins in physiology and disease. Nat Rev Drug Discov. 2021;20(5):384–405.
39. Weindel CG, Ellzey LM, Martinez EL, Watson RO, Patrick KL. Gasdermins gone wild: new roles for GSDMs in regulating cellular homeostasis. Trends Cell Biol. 2023;33(9):773–87.
40. Cristaldi M, Buscetta M, Cimino M, La Mensa A, Giuffrè MR, Fiore L, et al. Caspase-8 activation by cigarette smoke induces pro-inflammatory cell death of human macrophages exposed to lipopolysaccharide. Cell Death Dis. 2023;14(11):773.
41. Zhai Z, Yang F, Xu W, Han J, Luo G, Li Y, et al. Attenuation of rheumatoid arthritis through the Inhibition of Tumor Necrosis Factor-Induced Caspase 3/Gasdermin E-Mediated pyroptosis. Arthritis Rheumatol. 2022;74(3):427–40.
42. Lin PH, Lin HY, Kuo CC, Yang LT. N-terminal functional domain of gasdermin A3 regulates mitochondrial homeostasis via mitochondrial targeting. J Biomed Sci. 2015;22(1):44.
43. Wang H, Wang H, Chen J, Liu P, Xiao X. Overexpressed FAM111B degrades GSDMA to promote esophageal cancer tumorigenesis and cisplatin resistance. Cell Oncol (Dordr). 2024;47(1):343–59.
44. Terao C, Kawaguchi T, Dieude P, Varga J, Kuwana M, Hudson M, et al. Trans-ethnic meta-analysis identifies GSDMA and PRDM1 as susceptibility genes to systemic sclerosis. Ann Rheum Dis. 2017;76(6):1150–8.
45. Zhong X, Zeng H, Zhou Z, Su Y, Cheng H, Hou Y, et al. Structural mechanisms for regulation of GSDMB pore-forming activity. Nature. 2023;616(7957):598–605.
46. Rana N, Privitera G, Kondolf HC, Bulek K, Lechuga S, De Salvo C, et al. GSDMB is increased in IBD and regulates epithelial restitution/repair independent of pyroptosis. Cell. 2022;185(2):283–e9817.
47. Li X, Christenson SA, Modena B, Li H, Busse WW, Castro M, et al. Genetic analyses identify GSDMB associated with asthma severity, exacerbations, and antiviral pathways. J Allergy Clin Immunol. 2021;147(3):894–909.

48. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. Science. 2020;368(6494):eaaz7548.
49. Yan C, Niu Y, Li F, Zhao W, Ma L. System analysis based on the pyroptosis-related genes identifies GSDMC as a novel therapy target for pancreatic adenocarcinoma. J Transl Med. 2022;20(1):455.
50. Du J, Sarkar R, Li Y, He L, Kang W, Liao W, et al. N(6)-adenomethylation of GsdmC is essential for Lgr5(+) stem cell survival to maintain normal colonic epithelial morphogenesis. Dev Cell. 2022;57(16):1976–e948.
51. Hou J, Zhao R, Xia W, Chang CW, You Y, Hsu JM, et al. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. Nat Cell Biol. 2020;22(10):1264–75.
52. Yamagishi R, Kamachi F, Nakamura M, Yamazaki S, Kamiya T, Takasugi M, et al. Gasdermin D-mediated release of IL-33 from senescent hepatic stellate cells promotes obesity-associated hepatocellular carcinoma. Sci Immunol. 2022;7(72):eabl7209.
53. Burdette BE, Esparza AN, Zhu H, Wang S. Gasdermin D in pyroptosis. Acta Pharm Sin B. 2021;11(9):2768–82.
54. You J, Li X, Dai F, Liu J, Zhang Q, Guo W. GSDMD-mediated pyroptosis promotes cardiac remodeling in pressure overload. Clin Exp Hypertens. 2023;45(1):2189138.
55. Gaul S, Leszczynska A, Alegre F, Kaufmann B, Johnson CD, Adams LA, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. J Hepatol. 2021;74(1):156–67.
56. Song M, Wang J, Sun Y, Pang J, Li X, Liu Y, et al. Inhibition of gasdermin D-dependent pyroptosis attenuates the progression of silica-induced pulmonary inflammation and fibrosis. Acta Pharm Sin B. 2022;12(3):1213–24.
57. Jiang F, Jiang Q, Hou L, Zhao J, Zhu Z, Jia Q, et al. Inhibition of macrophage pyroptosis ameliorates silica-induced pulmonary fibrosis. Ecotoxicol Environ Saf. 2023;268:115693.
58. Li Y, Yuan Y, Huang ZX, Chen H, Lan R, Wang Z, et al. GSDME-mediated pyroptosis promotes inflammation and fibrosis in obstructive nephropathy. Cell Death Differ. 2021;28(8):2333–50.
59. Di M, Miao J, Pan Q, Wu Z, Chen B, Wang M, et al. OTUD4-mediated GSDME deubiquitination enhances radiosensitivity in nasopharyngeal carcinoma by inducing pyroptosis. J Exp Clin Cancer Res. 2022;41(1):328.
60. Ibrahim J, De Schutter E, Op de Beeck K. GSDME: a potential ally in Cancer Detection and Treatment. Trends Cancer. 2021;7(5):392–4.
61. Zhang CC, Li CG, Wang YF, Xu LH, He XH, Zeng QZ, et al. Chemotherapeutic paclitaxel and cisplatin differentially induce pyroptosis in A549 lung cancer cells via caspase-3/GSDME activation. Apoptosis. 2019;24(3–4):312–25.
62. Wei Z, Gao R, Sun Z, Yang W, He Q, Wang C, et al. Baicalin inhibits influenza A (H1N1)-induced pyroptosis of lung alveolar epithelial cells via caspase-3/GSDME pathway. J Med Virol. 2023;95(5):e28790.
63. Planès R, Pinilla M, Santoni K, Hessel A, Passemar C, Lay K, et al. Human NLRP1 is a sensor of pathogenic coronavirus 3CL proteases in lung epithelial cells. Mol Cell. 2022;82(13):2385–e4009.
64. Delmaghani S, del Castillo FJ, Michel V, Leibovici M, Aghaie A, Ron U, et al. Mutations in the gene encoding pejvakin, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. Nat Genet. 2006;38(7):770–8.
65. Delmaghani S, Defourny J, Aghaie A, Beurg M, Dulon D, Thelen N, et al. Hypervulnerability to sound exposure through impaired adaptive proliferation of Peroxisomes. Cell. 2015;163(4):894–906.
66. Defourny J, Aghaie A, Perfettini I, Avan P, Delmaghani S, Petit C. Pejvakin-mediated pexophagy protects auditory hair cells against noise-induced damage. Proc Natl Acad Sci U S A. 2019;116(16):8010–7.
67. Zhou J, Qiu J, Song Y, Liang T, Liu S, Ren C, et al. Pyroptosis and degenerative diseases of the elderly. Cell Death Dis. 2023;14(2):94.
68. He Z, Feng D, Zhang C, Chen Z, Wang H, Hou J, et al. Recent strategies for evoking immunogenic pyroptosis in antitumor immunotherapy. J Control Release. 2024;366:375–94.
69. Rao Z, Zhu Y, Yang P, Chen Z, Xia Y, Qiao C, et al. Pyroptosis in inflammatory diseases and cancer. Theranostics. 2022;12(9):4310–29.
70. Frank D, Vince JE. Pyroptosis versus necroptosis: similarities, differences, and crosstalk. Cell Death Differ. 2019;26(1):99–114.
71. Du T, Gao J, Li P, Wang Y, Qi Q, Liu X, et al. Pyroptosis, metabolism, and tumor immune microenvironment. Clin Transl Med. 2021;11(8):e492.
72. Shi J, Gao W, Shao F. Pyroptosis. Gasdermin-mediated programmed necrotic cell death. Trends Biochem Sci. 2017;42(4):245–54.
73. Choi EH, Park SJ. TXNIP: a key protein in the cellular stress response pathway and a potential therapeutic target. Exp Mol Med. 2023;55(7):1348–56.
74. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 Receptor in Infection and Inflammation. Immunity. 2017;47(1):15–31.
75. Huang X, Feng Y, Xiong G, Whyte S, Duan J, Yang Y, et al. Caspase-11, a specific sensor for intracellular lipopolysaccharide recognition, mediates the non-canonical inflammatory pathway of pyroptosis. Cell Biosci. 2019;9:31.
76. Liu P, Zhang Z, Chen H, Chen Q, Pyroptosis. Mechanisms and links with diabetic cardiomyopathy. Ageing Res Rev. 2024;94:102182.
77. Chen M, Rong R, Xia X. Spotlight on pyroptosis: role in pathogenesis and therapeutic potential of ocular diseases. J Neuroinflammation. 2022;19(1):183.
78. Ma M, Chai K, Deng R. Study of the correlation between the noncanonical pathway of pyroptosis and idiopathic inflammatory myopathy. Int Immunopharmacol. 2021;98:107810.
79. Van Opdenbosch N, Van Gorp H, Verdonckt M, Saavedra PHV, de Vasconcelos NM, Gonçalves A, et al. Caspase-1 Engagement and TLR-Induced c-FLIP expression suppress ASC/Caspase-8-Dependent apoptosis by Inflammasome Sensors NLRP1b and NLRC4. Cell Rep. 2017;21(12):3427–44.
80. Ai Y, Meng Y, Yan B, Zhou Q, Wang X. The biochemical pathways of apoptotic, necroptotic, pyroptotic, and ferroptotic cell death. Mol Cell. 2024;84(1):170–9.
81. Xiao F, Gao W, Wang X, Chen T. Amplification activation loop between caspase-8 and – 9 dominates artemisinin-induced apoptosis of ASTC-a-1 cells. Apoptosis. 2012;17(6):600–11.
82. Zhang Z, Zhang Y, Xia S, Kong Q, Li S, Liu X, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature. 2020;579(7799):415–20.
83. Orning P, Weng D, Starheim K, Ratner D, Best Z, Lee B, et al. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. Science. 2018;362(6418):1064–9.
84. Sarhan J, Liu BC, Muendlein HI, Li P, Nilson R, Tang AY, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. Proc Natl Acad Sci U S A. 2018;115(46):E10888–97.
85. Hänggi K, Ruffell B. Cell death, therapeutics, and the immune response in cancer. Trends Cancer. 2023;9(5):381–96.
86. Tong X, Tang R, Xiao M, Xu J, Wang W, Zhang B, et al. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. J Hematol Oncol. 2022;15(1):174.
87. Yan J, Wan P, Choksi S, Liu ZG. Necroptosis and tumor progression. Trends Cancer. 2022;8(1):21–7.
88. Zhang T, Wang Y, Inuzuka H, Wei W. Necroptosis pathways in tumorigenesis. Semin Cancer Biol. 2022;86(Pt 3):32–40.
89. Zhan C, Huang M, Yang X, Hou J. MLKL: functions beyond serving as the executioner of Necroptosis. Theranostics. 2021;11(10):4759–69.
90. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060–72.
91. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22(4):266–82.
92. Chen L, Min J, Wang F. Copper homeostasis and cuproptosis in health and disease. Signal Transduct Target Ther. 2022;7(1):378.
93. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol. 2021;18(5):1106–21.
94. Gao W, Wang X, Zhou Y, Wang X, Yu Y. Autophagy, ferroptosis, pyroptosis, and necroptosis in tumor immunotherapy. Signal Transduct Target Ther. 2022;7(1):196.
95. Hu X, Zhang H, Zhang Q, Yao X, Ni W, Zhou K. Emerging role of STING signalling in CNS injury: inflammation, autophagy, necroptosis, ferroptosis and pyroptosis. J Neuroinflammation. 2022;19(1):242.
96. Tang R, Xu J, Zhang B, Liu J, Liang C, Hua J, et al. Ferroptosis, necroptosis, and pyroptosis in anticancer immunity. J Hematol Oncol. 2020;13(1):110.
97. Yuan J, Ofengeim D. A guide to cell death pathways. Nat Rev Mol Cell Biol. 2023;25(5):379–95.
98. Malli F, Bardaka F, Tsilioni I, Karetsi E, Gourgoulianis KI, Daniil Z. 8-isoprostane levels in serum and bronchoalveolar lavage in idiopathic pulmonary fibrosis and sarcoidosis. Food Chem Toxicol. 2013;61:160–3.
99. Clynick B, Corte TJ, Jo HE, Stewart I, Glaspole IN, Grainge C, et al. Biomarker signatures for progressive idiopathic pulmonary fibrosis. Eur Respir J. 2022;59(3):2101181.
100. Rao LZ, Wang Y, Zhang L, Wu G, Zhang L, Wang FX, et al. IL-24 deficiency protects mice against bleomycin-induced pulmonary fibrosis by repressing IL-4-induced M2 program in macrophages. Cell Death Differ. 2021;28(4):1270–83.
101. Byrne AJ, Maher TM, Lloyd CM. Pulmonary macrophages: a New Therapeutic Pathway in Fibrosing Lung Disease? Trends Mol Med. 2016;22(4):303–16.

102. Luo J, Li P, Dong M, Zhang Y, Lu S, Chen M, et al. SLC15A3 plays a crucial role in pulmonary fibrosis by regulating macrophage oxidative stress. Cell Death Differ. 2024;31(4):417–30.
103. Zhou X, Zhang C, Yang S, Yang L, Luo W, Zhang W, et al. Macrophage-derived MMP12 promotes fibrosis through sustained damage to endothelial cells. J Hazard Mater. 2024;461:132733.
104. Xu Y, Ying L, Lang JK, Hinz B, Zhao R. Modeling mechanical activation of macrophages during pulmonary fibrogenesis for targeted anti-fibrosis therapy. Sci Adv. 2024;10(13):eadj9559.
105. Tian J, Song D, Peng Y, Zhang J, Ma L, Chen Z, et al. Silica-induced macrophage pyroptosis propels pulmonary fibrosis through coordinated activation of relaxin and osteoclast differentiation signaling to reprogram fibroblasts. Ecotoxicol Environ Saf. 2024;273:116106.
106. Li Y, Li H, Liu S, Pan P, Su X, Tan H, et al. Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Mol Immunol. 2018;99:134–44.
107. Cho SJ, Hong KS, Jeong JH, Lee M, Choi AMK, Stout-Delgado HW, et al. DROSHA-Dependent AIM2 inflammasome activation contributes to lung inflammation during idiopathic pulmonary fibrosis. Cells. 2019;8(8):938.
108. Stout-Delgado HW, Cho SJ, Chu SG, Mitzel DN, Villalba J, El-Chemaly S, et al. Age-Dependent susceptibility to Pulmonary Fibrosis is Associated with NLRP3 inflammasome activation. Am J Respir Cell Mol Biol. 2016;55(2):252–63.
109. Ruan H, Li X, Zhou L, Zheng Z, Hua R, Wang X, et al. Melatonin decreases GSDME mediated mesothelial cell pyroptosis and prevents peritoneal fibrosis and ultrafiltration failure. Sci China Life Sci. 2024;67(2):360–78.
110. Sharma BR, Kanneganti TD. NLRP3 inflammasome in cancer and metabolic diseases. Nat Immunol. 2021;22(5):550–9.
111. Jiang H, Gao H, Wang Q, Wang M, Wu B. Molecular mechanisms and clinical application of Iguratimod: a review. Biomed Pharmacother. 2020;122:109704.
112. Liu W, Han X, Li Q, Sun L, Wang J. Iguratimod ameliorates bleomycin-induced pulmonary fibrosis by inhibiting the EMT process and NLRP3 inflammasome activation. Biomed Pharmacother. 2022;153:113460.
113. Nie Y, Li J, Zhai X, Wang Z, Wang J, Wu Y, et al. Elamipretide(SS-31) attenuates idiopathic pulmonary fibrosis by inhibiting the Nrf2-Dependent NLRP3 inflammasome in macrophages. Antioxid (Basel). 2023;12(12):2022.
114. Abd Elrazik NA, Helmy SA. Betanin protects against bleomycin-induced pulmonary fibrosis by regulating the NLRP3/IL-1β/TGF-β1 pathway-mediated epithelial-to-mesenchymal transition. Food Funct. 2024;15(1):284–94.
115. Liu Y, Chen S, Yu L, Deng Y, Li D, Yu X, et al. Pemafibrate attenuates pulmonary fibrosis by inhibiting myofibroblast differentiation. Int Immunopharmacol. 2022;108:108728.
116. Banerjee S, High J, Stirling S, Shepstone L, Swart AM, Telling T, et al. Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial. Lancet. 2021;398(10310):1487–97.
117. Abdelhady R, Cavalu S, Saber S, Elmowafy R, Morsy NE, Ibrahim S, et al. Mirtazapine, an atypical antidepressant, mitigates lung fibrosis by suppressing NLPR3 inflammasome and fibrosis-related mediators in endotracheal bleomycin rat model. Biomed Pharmacother. 2023;161:114553.
118. Coll RC, Hill JR, Day CJ, Zamoshnikova A, Boucher D, Massey NL, et al. MCC950 directly targets the NLRP3 ATP-hydrolysis motif for inflammasome inhibition. Nat Chem Biol. 2019;15(6):556–9.
119. Ward R, Li W, Abdul Y, Jackson L, Dong G, Jamil S, et al. NLRP3 inflammasome inhibition with MCC950 improves diabetes-mediated cognitive impairment and vasoneuronal remodeling after ischemia. Pharmacol Res. 2019;142:237–50.
120. Zhou Y, Du T, Yang CL, Li T, Li XL, Liu W, et al. Extracellular vesicles encapsulated with caspase-1 inhibitor ameliorate experimental autoimmune myasthenia gravis through targeting macrophages. J Control Release. 2023;364:458–72.
121. Liang H, Sun Y, Gao A, Zhang N, Jia Y, Yang S, et al. Ac-YVAD-cmk improves neurological function by inhibiting caspase-1-mediated inflammatory response in the intracerebral hemorrhage of rats. Int Immunopharmacol. 2019;75:105771.
122. Audia JP, Yang XM, Crockett ES, Housley N, Haq EU, O'Donnell K, et al. Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y(12) receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. Basic Res Cardiol. 2018;113(5):32.
123. Tao H, Zhao H, Mo A, Shao L, Ge D, Liu J, et al. VX-765 attenuates silica-induced lung inflammatory injury and fibrosis by modulating alveolar macrophages pyroptosis in mice. Ecotoxicol Environ Saf. 2023;249:114359.
124. Chen WC, Yu WK, Su VY, Hsu HS, Yang KY. NLRP3 Inflammasome activates endothelial-to-mesenchymal transition via focal adhesion kinase pathway in Bleomycin-Induced Pulmonary Fibrosis. Int J Mol Sci. 2023;24(21):15813.
125. Hu JJ, Liu X, Xia S, Zhang Z, Zhang Y, Zhao J, et al. FDA-approved disulfiram inhibits pyroptosis by blocking gasdermin D pore formation. Nat Immunol. 2020;21(7):736–45.
126. Silva CMS, Wanderley CWS, Veras FP, Sonego F, Nascimento DC, Gonçalves AV, et al. Gasdermin D inhibition prevents multiple organ dysfunction during sepsis by blocking NET formation. Blood. 2021;138(25):2702–13.
127. Hu X, Zou M, Zheng W, Zhu M, Hou Q, Gao H, et al. Bhlhe40 deficiency attenuates LPS-induced acute lung injury through preventing macrophage pyroptosis. Respir Res. 2024;25(1):100.
128. Sun L, Wang H, Wang Z, He S, Chen S, Liao D, et al. Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell. 2012;148(1–2):213–27.
129. Rathkey JK, Zhao J, Liu Z, Chen Y, Yang J, Kondolf HC, et al. Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis. Sci Immunol. 2018;3(26):eaat2738.
130. Ueda S, Chen-Yoshikawa TF, Tanaka S, Yamada Y, Nakajima D, Ohsumi A, et al. Protective effect of necrosulfonamide on rat pulmonary ischemia-reperfusion injury via inhibition of necroptosis. J Thorac Cardiovasc Surg. 2022;163(2):e113–22.
131. Itano J, Taniguchi A, Senoo S, Asada N, Gion Y, Egusa Y, et al. Neuropeptide Y antagonizes development of pulmonary fibrosis through IL-1β inhibition. Am J Respir Cell Mol Biol. 2022;67(6):654–65.
132. Garon EB, Lu S, Goto Y, De Marchi P, Paz-Ares L, Spigel DR, et al. Canakinumab as Adjuvant Therapy in patients with completely resected non-small-cell Lung Cancer: results from the CANOPY-A Double-Blind, randomized clinical trial. J Clin Oncol. 2024;42(2):180–91.
133. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, et al. Canakinumab for the treatment of Autoinflammatory recurrent fever syndromes. N Engl J Med. 2018;378(20):1908–19.
134. Tall AR, Bornfeldt KE. Inflammasomes and atherosclerosis: a mixed picture. Circ Res. 2023;132(11):1505–20.
135. Rogliani P, Calzetta L, Ora J, Matera MG. Canakinumab for the treatment of chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2015;31:15–27.
136. Kraft L, Erdenesukh T, Sauter M, Tschöpe C, Klingel K. Blocking the IL-1β signalling pathway prevents chronic viral myocarditis and cardiac remodeling. Basic Res Cardiol. 2019;114(2):11.
137. Alehashemi S, Dasari S, Metpally A, Uss K, Castelo-Soccio LA, Heller T, et al. Anakinra-Associated Systemic Amyloidosis Arthritis Rheumatol. 2024;76(1):100–6.
138. Abbasi M, Mousavi MJ, Jamalzehi S, Alimohammadi R, Bezvan MH, Mohammadi H, et al. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol. 2019;234(7):10018–31.
139. Brucato A, Imazio M, Gattorno M, Lazaros G, Maestroni S, Carraro M, et al. Effect of Anakinra on recurrent Pericarditis among patients with Colchicine Resistance and Corticosteroid Dependence: the AIRTRIP Randomized Clinical Trial. JAMA. 2016;316(18):1906–12.
140. Dember LM, Hung A, Mehrotra R, Hsu JY, Raj DS, Charytan DM, et al. A randomized controlled pilot trial of anakinra for hemodialysis inflammation. Kidney Int. 2022;102(5):1178–87.
141. Fritzsching B, Zhou-Suckow Z, Trojanek JB, Schubert SC, Schatterny J, Hirtz S, et al. Hypoxic epithelial necrosis triggers neutrophilic inflammation via IL-1 receptor signaling in cystic fibrosis lung disease. Am J Respir Crit Care Med. 2015;191(8):902–13.
142. Puccetti M, Pariano M, Stincardini C, Wojtylo P, Schoubben A, Nunzi E, et al. Pulmonary drug delivery technology enables anakinra repurposing in cystic fibrosis. J Control Release. 2023;353:1023–36.
143. Nan D, Abraira-Meriel C, de la Roz-Fernández S, Maestre-Orozco T, Hernandez JL, Fernandez-Ayala M. Delayed use of the recombinant human IL-1 receptor antagonist Anakinra in five COVID-19 patients with pulmonary fibrosis and persistent hypoxaemia: a preliminary Report. Eur J Case Rep Intern Med. 2021;8(10):002821.
144. Duecker R, Baer P, Eickmeier O, Strecker M, Kurz J, Schaible A, et al. Oxidative stress-driven pulmonary inflammation and fibrosis in a mouse model of human ataxia-telangiectasia. Redox Biol. 2018;14:645–55.
145. Tong J, Lan XT, Zhang Z, Liu Y, Sun DY, Wang XJ, et al. Ferroptosis inhibitor liproxstatin-1 alleviates metabolic dysfunction-associated fatty liver disease in mice: potential involvement of PANoptosis. Acta Pharmacol Sin. 2023;44(5):1014–28.

146. Tao N, Li K, Liu J, Fan G, Sun T. Liproxstatin-1 alleviates bleomycin-induced alveolar epithelial cells injury and mice pulmonary fibrosis via attenuating inflammation, reshaping redox equilibrium, and suppressing ROS/p53/α-SMA pathway. Biochem Biophys Res Commun. 2021;551:133–9.
147. Franks ME, Macpherson GR, Figg WD. Thalidomide Lancet. 2004;363(9423):1802–11.
148. Chang HW, Sim KH, Lee YJ. Thalidomide attenuates mast cell activation by upregulating SHP-1 signaling and interfering with the action of CRBN. Cells. 2023;12(3):469.
149. Dsouza NN, Alampady V, Baby K, Maity S, Byregowda BH, Nayak Y. Thalidomide interaction with inflammation in idiopathic pulmonary fibrosis. Inflammopharmacology. 2023;31(3):1167–82.
150. Dong X, Li X, Li M, Chen M, Fan Q, Wei W. Antiinflammation and antioxidant effects of Thalidomide on Pulmonary Fibrosis in mice and human lung fibroblasts. Inflammation. 2017;40(6):1836–46.
151. Missiroli S, Perrone M, Gafà R, Nicoli F, Bonora M, Morciano G, et al. PML at mitochondria-associated membranes governs a trimeric complex with NLRP3 and P2X7R that modulates the tumor immune microenvironment. Cell Death Differ. 2023;30(2):429–41.
152. Cui L, Tan YJ, Xu SQ, Qin BF, Xiu MX, Zhang X, et al. Ginsenoside Rd, a natural production for attenuating fibrogenesis and inflammation in hepatic fibrosis by regulating the ERRα-mediated P2X7r pathway. Food Funct. 2023;14(12):5606–19.
153. Raffaghello L, Principi E, Baratto S, Panicucci C, Pintus S, Antonini F, et al. P2X7 Receptor Antagonist Reduces Fibrosis and Inflammation in a Mouse Model of Alpha-Sarcoglycan Muscular Dystrophy. Pharmaceuticals (Basel). 2022;15(1):89.
154. Jiang S, Zhang Y, Zheng JH, Li X, Yao YL, Wu YL, et al. Potentiation of hepatic stellate cell activation by extracellular ATP is dependent on P2X7R-mediated NLRP3 inflammasome activation. Pharmacol Res. 2017;117:82–93.
155. Gabillard-Lefort C, Casey M, Glasgow AMA, Boland F, Kerr O, Marron E, et al. Trikafta Rescues CFTR and Lowers Monocyte P2X7R-induced Inflammasome Activation in Cystic Fibrosis. Am J Respir Crit Care Med. 2022;205(7):783–94.

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