

Role of Pyroptosis in Respiratory Diseases and its Therapeutic Potential

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Abstract: Pyroptosis is an inflammatory type of regulated cell death that is dependent on inflammasome activation and downstream proteases such as caspase-1 or caspase 4/5/11. The main executors are gasdermins, which have an inherent pore-forming function on the membrane and release inflammatory cytokines, such as interleukin (IL)-1 β , IL-18 and high mobility group box 1. Emerging evidence demonstrates that pyroptosis is involved in the pathogenesis of various pulmonary diseases. In this review, we mainly discuss the biological mechanisms of pyroptosis, explore the relationship between pyroptosis and respiratory diseases, and discuss emerging therapeutic strategies for respiratory diseases.

Keywords: pyroptosis, pulmonary disease, caspase-1, caspase-4/5/11, gasdermins

Introduction

Pyroptosis is a newly discovered type of regulated cell death that was first described in *Salmonella*-infected macrophages and dendritic cells.¹ The morphological characteristics of pyroptosis which are distinguishable from necroptosis include cell membrane pore formation, cytomembrane fracture, cellular swelling, chromatin condensation, and increased inflammatory cytokine production. However, in contrast to apoptosis, the integrity of the mitochondria is maintained, and pyroptosis has no effect on the release of cytochrome C.¹⁻³ Pyroptosis was initially reported to occur in innate immune cells, such as macrophages, dendritic cells, and neutrophils. However, recent studies have demonstrated that pyroptosis can also occur in epithelial cells, endothelial cells, keratinocytes, and neurons.⁴

Pyroptosis was initially described as an inflammatory type of regulated cell death mediated by caspase-1 which belongs to the inflammatory caspase family and is activated by inflammasome.⁵ An inflammasome is an intracellular multi-protein compound, which mainly includes the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) and PYHIN protein families.⁶ The inflammasomes can be activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs).⁷ Bioactive caspase-1 can process gasderminD (GSDMD) into a GSDMD N-terminal (GSDMD-NT) fragment and cleave pro-IL-1 β and pro-IL-18 into mature IL-1 β and IL-18, eventually leading to canonical pyroptosis and the release many inflammatory cytokines.⁷

Lipopolysaccharides (LPS) from gram-negative bacteria can directly bind to caspase-4/5/11 independent of caspase-1 to induce pyroptosis, and this is described as the non-canonical pyroptosis pathway.⁸ In 2015, it was discovered that GSDMD is an executor of pyroptosis, N terminal of GSDMD can form pores on the plasma membrane, thereby releasing many inflammatory cytokines, pro-fibrotic cytokines, and cell contents.^{9,10} Notably, other gasdermin family members (such as GSDMA, GSDMB, GSDMC, and GSDME) have been increasingly involved in cell membrane pore formation and pyroptosis induction.¹¹⁻¹⁴ Therefore, the Nomenclature Committee on Cell Death modified the definition of pyroptosis, and it is now described as a cell death dependent on the gasdermin family's participation in membrane pore formation.¹⁵

Pyroptosis is involved in the development of various diseases, such as cancer, and autoimmune, metabolic, and nervous system diseases.^{16–19} Emerging evidence has confirmed that Dermatophagoides farina 1 (Der f1)-induced pyroptosis in human bronchial epithelia contributes to the development of asthma.²⁰ In addition, inflammasome-mediated pyroptosis participates in the pathogenesis of pulmonary infections, pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD).^{21–24} Therefore, the role of pyroptosis in pulmonary diseases, particularly, in the development of novel diagnostic and therapeutic methods to manage these diseases, has become a research focus.

This review highlights the signaling pathway and inhibitors involved in pyroptosis and the relationship between pyroptosis and pulmonary diseases. It also discusses potential therapeutic targets related to pyroptosis in pulmonary diseases.

Molecular Mechanisms of Pyroptosis

Components of the Inflammasome

The inflammasome is an intracellular multi-protein compound consisting of a sensor protein (for example, pattern recognition receptors [PRRs]), apoptosis-associated speck like protein containing a caspase recruitment domain (ASC) and a caspase-1 family protease.²⁵ PRRs can identify PAMPs or DAMPs and include the NLR family (NLRP3, and NLR family caspase recruitment domain [CARD] containing proteins, such as NLRC1, NLRC4, and NLRC6) localized in the cytoplasm, which is present within the plasma membrane or lysosomal organelles and PYHIN protein family including absent in melanoma (AIM2).^{26,27} NLR proteins consist of C-terminal leucine-rich repeats (LRRs), a central NOD/NACHT, and an N-terminal CARD or pyrin domain (PYD). The NOD/NACHT domain is shared by the NLR family and its downstream pathway is activated by adenosine triphosphate (ATP)-dependent oligomerization. LRRs are associated with ligand sensing and autoregulation, and the CARD and PYD domains interact with the downstream signals.²⁸ Of note, NLRP3 has been identified as a crucial NLR family member, which recognizes PAMPs (such as bacteria, viruses, and fungi) or DAMPs (eg ATP and uric acid).²⁶ Other NLR family members include NLRP1, which is activated by the anthrax lethal toxin;²⁹ NLRC4, which is activated by cytosolic bacterial flagellin, such as that of *Salmonella*;³⁰ and NLRP6, which is activated by microbes, such as *Porphyromonas gingivalis*.³¹ AIM2 proteins typically contain a DNA-binding HIN-200 domain and a PYD-signaling domain, which specifically recognize cytoplasmic double-stranded DNA.²⁷ Pyrin is encoded by the *MEFV* gene, which has four functional domains; PYD, and the zinc finger, coiled coil, and B30.2/SPRY domains. It specifically recognizes RhoA guanosine triphosphatase inactivation induced by pathogens.³² ASC is an essential intermediate protein that combines sensor proteins (NLRs and AIM2) and caspase-1, whereas NLRC4 is an exception. NLRC4 activates caspase-1 by directly recruiting pro-caspase-1.^{6,33}

Canonical inflammasome activation requires two independent steps. Taking the activation of the NLRP3 inflammasome as an example, the first step is priming, which is induced by the Toll-like receptor (TLR)/myeloid differentiation primary response 88 (MyD88)-nuclear factor kappa B (NF- κ B) signaling pathway to upregulate the transcription of *NLRP3*, *pro-IL-1 β* and *pro-IL-18*.^{6,7,25,34} The second step involves formation and modification of the NLRP3 inflammasome. There are three classic activation pathways of the NLRP3 inflammasome. (i) potassium efflux,³⁵ which is a mutual pathway for the assembly of the NLRP3 inflammasome which promotes the interaction between NEK7-NLRP3.^{36,37} (ii) lysosomes damage.^{35,38} (iii) the generation of mitochondrial reactive oxygen species (ROS),^{7,35} mitochondrial ROS promotes the dissociation of thioredoxin from thioredoxin-interacting protein (TXNIP). Subsequently, TXNIP can bind to NLRP3 and trigger the activation of the NLRP3 inflammasome by stimulating the recruitment of ASC and caspase-1.³⁹ Pro-caspase-1 is activated by inflammasomes to form bioactive caspase-1. Caspase-1 can cut the precursors of downstream inflammatory cytokines (such as pro IL-1 β and pro IL-18) and turn them into bioactive cytokines (IL-1 β and IL-18).

Non-canonical NLRP3 inflammasome activation has been recently discovered, and it is associated with potassium efflux.^{40–42} Potassium efflux via GSDMD pores in caspase-4/5/11-mediated non-classical pyroptosis is essential for NLRP3 inflammasome activation.⁴¹ Another study showed that LPS-induced caspase-11 activation triggered cleavage of the pannexin-1 channel, which promoted the release of ATP. ATP triggers P2X7, a purinoreceptor, to form a channel for potassium efflux, and subsequently, the NLRP3 inflammasome is activated.⁴² Emerging evidence has demonstrated that

caspase-8 is associated with NLRP3 inflammasome activation by promoting the formation of ASC and activation of caspase-1, and is also possibly related to potassium efflux.⁴³

Caspase Family Proteases

Caspase-1/4/5 and caspase-1/11 expressed in humans and mice, respectively, are the main caspase family proteases associated with pyroptosis.⁴⁴ Caspase-1 exists as an inert precursor in the cytoplasm, which can be activated by inflammasomes and can promote apoptosis and mediate the canonical pyroptosis pathway.⁴⁵ Caspase-1 proteolytically cleaves the precursor pro-IL-1 β /pro-IL-18 to generate mature IL-1 β /IL-18 and cleaves GSDMD into a 31kD N-terminal and a 22kD C-terminal. GSDMD-NT forms pores on the cell membrane, thus, inducing pyroptosis and releasing IL-1 β , IL-18, IL-1 α and high mobility group box 1 (HMGB1).⁴⁶

Caspase-4/5/11 are involved in the non-canonical pyroptosis pathway. CARD in caspase-4/5/11 recognizes LPS lipid A and induces the oligomerization of the caspases. Activated caspase-4/5/11 cleave GSDMD and release the GSDMD-NT fragment to induce cell membrane pore formation, release IL-1 α and HMGB1, and lead to pyroptosis.^{9,44} However, caspase-4/5/11-mediated pyroptosis has no effect on the processing of IL-1 β and IL-18. Interestingly, caspase-4/5/11 triggers non-canonical NLRP3 inflammasome activation to promote IL-1 β and IL-18 secretion.⁹

An increasing number of caspase family members have been found to play a role in pyroptosis. Caspase-3 was previously known as an executor of apoptosis, and emerging evidence has demonstrated that activated caspase-3 cleaves GSDME, thereby releasing the GSDME N-terminal and triggering pyroptosis.^{14,47,48} Caspase-3 is activated by caspase-8 through the death receptor pathway and can also be activated by caspase-9 via the mitochondrial apoptotic pathway.^{48,49} Various death stimuli or viral infections can result in permeabilization of the mitochondrial outer membrane, leading to the release of cytochrome C, which promotes the activation of caspase-9 which then cleaves caspase-3.⁴⁸ Emerging evidence suggests that caspase-1/3/7 cleave GSDME to generate GSDME-N terminal and induce pyroptosis in teleosts, and GSDME is cleaved by caspase-1 with high efficiency and by caspase-3 and 7 with less efficiency.⁵⁰ Furthermore, caspase-8 is considered a molecular switch for pyroptosis.^{51–53} Previous studies have demonstrated that caspase-8 triggers the formation of ASC specks, activation of caspase-1, and subsequent activation of the NLRP3 inflammasome, leading to pyroptosis in bone marrow-derived macrophages (BMDMs) and intestinal epithelial cells.⁵¹ Sarhan et al found that caspase-8 could cleave both GSDMD and GSDME, resulting in pyroptosis in murine macrophages during *Yersinia* infections.⁵² A recent study claimed that caspase-8 directly cleaves GSDMD to trigger pyroptosis, which provides the host defense against *Yersinia* infections.⁵³ Therefore, caspase-3/7/8 can also mediate pyroptosis.

Gasdermins: Executioners of Pyroptosis

Gasdermins are a family of pore-forming effector proteins that increase membrane permeabilization and induce pyroptosis. The gasdermin family is encoded by six paralogous genes in humans: *GSDMA*, *GSDMB*, *GSDMC*, *GSDMD*, *GSDME*, and *PJVK*, and nine genes in mice: *Gsdma* 1–3, *Gsdmc* 1–4, *Gsdme* and *pjvk*.¹⁰ The gasdermin family is composed of a cytotoxic N-terminal domain and a C-terminal inhibitory domain, and is linked by a long loop in the middle.¹⁰ This structure is shared by all gasdermin family members except for PJVK, which has a truncated C-terminal domain.⁵⁴

GSDMD is an executor of pyroptosis.⁹ Activated caspase-1/4/5/11 acts on the aspartic acid site on the circle to cleave GSDMD into two fragments: a 31-kDa GSDMD-NT fragment with an inherent pore-forming function and a 22-kDa GSDMD C-terminal (GSDMD-CT) fragment, which has an autoinhibitory role in the GSDMD-NT fragment.^{9,10} The GSDMD-NT fragment can target, using cardiolipin and phosphoinositides, the membrane to destroy its structure by forming pores with a diameter of 10–14nm and inducing pyroptosis.⁵⁵ Recent studies found that caspase-8 can cleave GSDMD into GSDMD-NT and GSDMD-CT fragments and induce pyroptosis.^{43,52,53} The pathway leading to GSDMD activation extends beyond the caspase family, and emerging evidence has demonstrated that neutrophil elastase can cleave GSDMD in active neutrophils.^{56,57} Although the site cleaved by neutrophil elastase is different from that of caspases, GSDMD still generates a fragment with pore-forming functions.⁵⁷

An increasing number of gasdermin family members have been found to play a role in pyroptosis. GSDME cleaved by caspase-3 can induce pyroptosis.^{47,48} Rogers et al revealed that caspase-3 cleaved GSDME at Asp270 and divided into

N-terminal and C-terminal fragments. The N-terminus of GSDME has the same function as GSDMD-NT, which has intrinsic pore-forming activity and induces pyroptosis in apoptotic cells, but is not scavenged.⁴⁸ Wang et al claimed that GSDME cleaved by caspase-3 can switch from apoptosis, induced by tumor necrosis factor alpha (TNF- α) or chemotherapy drugs, to pyroptosis, and GSDME-/- mice are protected from chemotherapy-induced tissue damage.⁵⁸ A study of pyroptosis in teleosts suggested that GSDME, which is the only gasdermin family member present in teleosts, triggers pyroptosis, and GSDME is cleaved by caspase-1/3/7, all of which occur at the FEVD site in the linker region of GSDME.⁵⁰

GSDMA acts as an effector of epithelial pyroptosis during *Streptococcus pyogenes* infections, and the cysteine protease SpeB of *Streptococcus pyogenes* cleaves GSDMA in the linker region after Gln246 and generates N-terminus of GSDMA, triggering pyroptosis.¹¹

In 2020, Feng et al claimed that GSDMB was cleaved by lymphocyte-derived granzyme A to induce pyroptosis in natural killer cells and cytotoxic T lymphocytes.¹² GSDMB is highly expressed in various tissues, especially in the digestive tract epithelia, including derived tumors. GSDMB cleaved by granzyme A-induced pyroptosis promotes tumor clearance in mice, and may enhance anti-tumor immunity.¹²

Hou et al revealed that the N-terminus of GSDMC also induces pyroptosis, and GSDMC is cleaved by caspase-8.⁵⁹ Phosphorylated signal transducer and activator of transcription 3 interacts with programmed death ligand 1 and promotes its nuclear translocation, which upregulates GSDMC transcription under hypoxic conditions. GSDMC is cleaved by caspase-8 under TNF- α treatment, thereby switching from apoptosis to pyroptosis and facilitating tumor necrosis.¹³ Although the N-terminus of GSDMA, GSDMB, GSDMC, and GSDME also drive cells to undergo pyroptosis, GSDMD is still the best characterized executor of pyroptosis.

Canonical (Caspase-1-Mediated) Pyroptosis Pathway

The canonical pyroptosis signaling pathway is triggered by inflammasomes, mainly the NLR family and pyrin protein families. Inflammasomes can be activated by different stimulants, such as PAMPs or DAMPs.⁷ Caspase-1 is triggered by the inflammasome and pro-IL-1 β /pro-IL-18 is converted to IL-1 β /IL-18 via caspase-1. Simultaneously, caspase-1 cleaves GSDMD and releases the GSDMD-NT.⁵ The GSDMD-NT fragment forms pores on the cytomembrane and promotes the secretion of the inflammatory cytokines, IL-1 β , IL-18, IL-1 α and HMGB1, resulting in plasma membrane rupture, cellular swelling, and eventually cell death (pyroptosis) (Figure 1).⁹

Non-Canonical (Caspase-4/5/11-Mediated) Pyroptosis Pathway

The non-canonical pyroptosis pathway was initially thought to be mediated by caspase-4/5/11. LPS from gram-negative bacteria can access the cell cytoplasm via CD14/TLR4/MD2 receptor-mediated endocytosis or bacterial outer membrane vesicles and bind directly to caspase-4/5/11.^{40,60} The CARD in caspase-4/5/11 recognizes lipid A, which is the most conserved region in LPS, and induces oligomerization of caspases.⁹ Activated caspase-4/5/11 cleaves GSDMD into a GSDMD-NT fragment to induce cell membrane pore formation and initiate pyroptosis. However, caspase-4/5/11-mediated pyroptosis cannot release IL-1 β and IL-18, in contrast to the caspase-1-mediated classical pyroptosis pathway. Interestingly, caspase-4/5/11 triggers non-canonical NLRP3 inflammasome activation through a cell-intrinsic process to promote IL-1 β and IL-18 secretion (Figure 1).^{41,42,61}

Other Pyroptosis Pathways

In 2017, it was discovered that the caspase-3/GSDME pathway induces pyroptosis.⁴⁸ GSDME, cleaved by caspase-3 during apoptosis, mediates the switch to pyroptosis. Furthermore, caspase-3/GSDME-mediated pyroptosis is involved in chemotherapy-induced tissue damage, providing a new target for the treatment of cancer.⁵⁸ A recent study revealed that cleavage of GSDME by caspase-1/3/7 is the only pathway that induces pyroptosis in teleosts.⁵⁰

The mechanism underlying caspase-8-mediated pyroptosis is complex. Caspase-8 induces pyroptosis by activating the NLRP3 inflammasome.⁵¹ Another report claims that caspase-8 cleaves GSDMD and releases GSDMD-NT to trigger pyroptosis.⁵³ Interestingly, a recent study has demonstrated that caspase-8 could cleave both GSDMD and GSDME and release their N-terminal fragments, thus inducing pyroptosis.⁵² The cleavage of GSDMA by the cysteine protease SpeB triggers pyroptosis during *Streptococcus pyogenes* infections.¹¹ GSDMB cleaved by granzyme A as an effector of

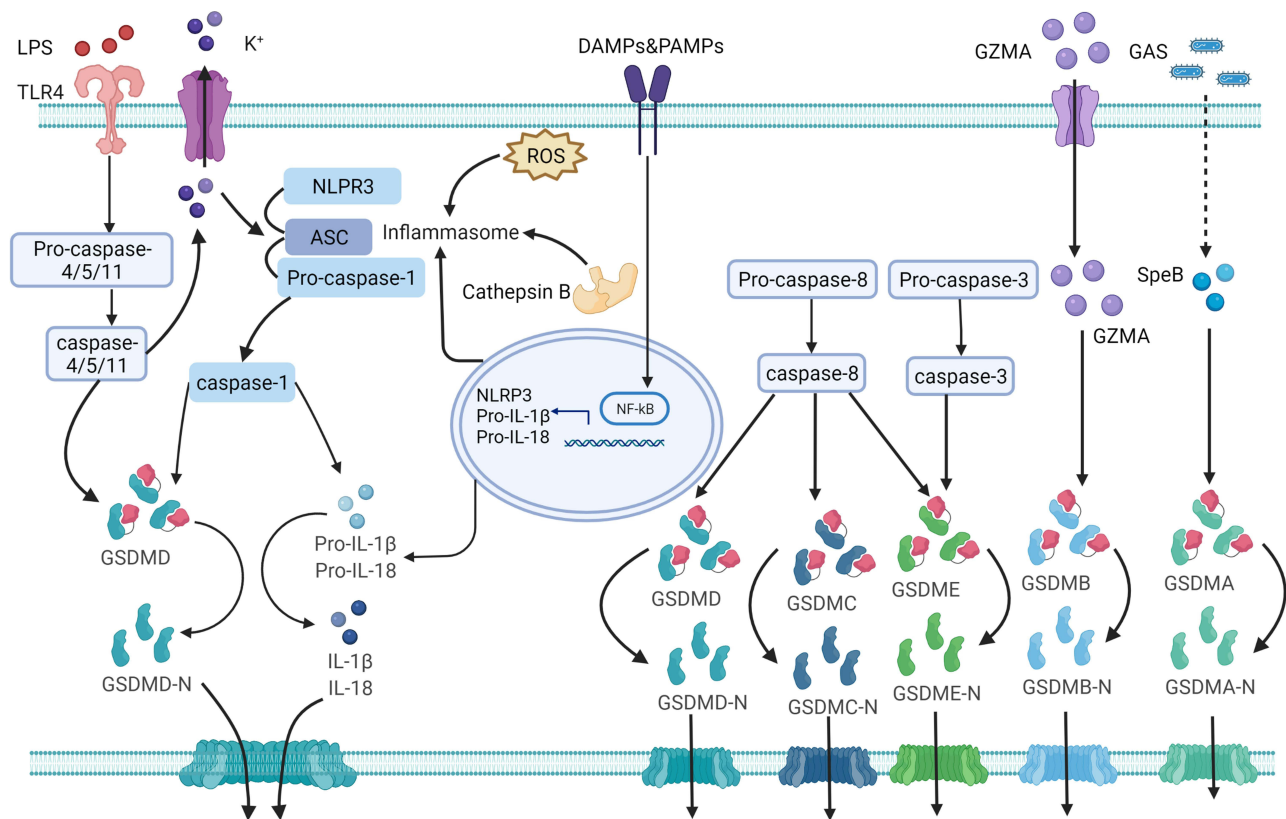


Figure 1 The mechanism of pyroptosis. Pyroptosis involves canonical, non-canonical, and other pathways. NLRP3 inflammasome activation requires DAMPs or PAMPs to trigger the NF- κ B-mediated upregulation of the transcription of *NLRP3*, *pro-IL-1 β* and *pro-IL-18*. The formation and modification of NLRP3 inflammasomes by potassium efflux, the generation of reactive oxygen species (ROS), and cathepsin B released by lysosomal damage. Caspase-1 is triggered by the inflammasome and pro-IL-1 β /pro-IL-18 is converted to IL-1 β /IL-18 via caspase-1. Simultaneously, caspase-1 cleaves GSDMD and releases the GSDMD-NT. The GSDMD-NT fragment forms pores on the cytomembrane and promotes the secretion of the inflammatory cytokines, IL-1 β and IL-18, resulting in plasma membrane rupture, cellular swelling, and eventually pyroptosis. LPS from gram-negative bacteria can access the cell cytoplasm via TLR4 receptor-mediated endocytosis and bind directly to caspase-4/5/11. Activated caspase-4/5/11 cleaves GSDMD into a GSDMD-NT fragment to induce cell membrane pore formation and initiate pyroptosis. This process can also cause NLRP3 activation by potassium efflux via nonselective pores. The cysteine protease (SpeB) from group A *Streptococcus* (GAP) can cleave GSDMA, triggering pyroptosis. The cleavage of GSDMA by the cysteine protease (SpeB), triggers pyroptosis during *Streptococcus pyogenes* infections. Active caspase-3 cleaves GSDME and releases GSDME-NT, thereby triggering pyroptosis. Caspase-8 can cleave GSDMD, GSDME, and GSDMC, to trigger pyroptosis.

pyroptosis mainly occurs in natural killer cells and cytotoxic T lymphocytes and is involved in the pathogenesis of gastrointestinal tumors.¹² Furthermore, caspase-8/GSDMC mediates a non-classical pyroptosis pathway in cancer cells, resulting in tumor necrosis (Figure 1).¹³

Role of Pyroptosis in Respiratory Diseases

Emerging evidence has revealed that pyroptosis is a key process for various diseases, including autoimmune diseases (eg cryptothermal protein-associated cycle syndrome, rheumatoid arthritis, and Crohn's disease),^{62,63} nervous system diseases (eg Alzheimer's disease and Parkinson's disease),^{64,65} metabolic diseases (eg gout and type II diabetes),^{66,67} atherosclerosis,⁶⁸ and cancer (eg colon cancer, breast cancer and melanoma).^{69,70} The role of pyroptosis in respiratory diseases has received considerable attention. Pyroptosis is relevant to the pathogenesis of respiratory diseases, whether as a positive or negative regulator. Therefore, we illuminate the role of pyroptosis in several respiratory diseases, including COPD, asthma, acute respiratory distress syndrome (ARDS), pulmonary fibrosis, lung cancer, and pulmonary infection.

COPD

COPD is a heterogeneous disease characterized by irreversible airflow obstruction, involving chronic inflammation of the small airways and lung parenchyma, which causes small airway fibrosis and emphysema.⁷¹ COPD is predicted to become the third leading cause of death and the fifth leading cause of economic burdens worldwide.⁷² Despite intense research

efforts focused on the pathogenesis and therapy of COPD, the pathogenesis of COPD has not been fully elucidated, and only a few therapies can lower mortality rates and exacerbations in patients with COPD. Infection, exposure to toxic particles, air pollution and cigarette smoke (CS) are the major causes of COPD.

CS is a major cause of COPD worldwide. Increased inflammasome activation, ASC speck accumulation, and IL-1 β expression are observed in the lungs of patients with COPD, as well as in experimental models including murine models of COPD.^{73–75} Furthermore, the NLRP3 inflammasome was upregulated in an in vitro model of COPD exacerbation, and it may serve as a novel biomarker in the diagnosis of COPD exacerbation and as a new target for therapies.⁷⁶ However, another report revealed that NLRP3 inflammasome had no correlation with the severity of stable COPD patients, possibly due to the increased expression of the inflammatory and inflammasome inhibitory molecules IL-37 and NALP7.⁷⁷ These studies indicate that inflammasome activation and expression of IL-1 β may play important roles in the pathogenesis of COPD, whereas the role of pyroptosis in the pathogenesis of COPD has been poorly studied.

A recent study indicated that CS-induced pyroptosis occurs via the ROS/NLRP3 inflammasome pathway in bronchial epithelial cells. Moreover, the caspase-1 inhibitor, VX-765, can inhibit pyroptosis in bronchial epithelial cells, and the ROS inhibitor, N-acetyl-L-cysteine, inhibits the activation of NLRP3 inflammasome and production of IL-1 β and IL-18.⁷⁸ Emerging evidence has revealed that triggering receptor expressed on myeloid cells (TREM-1) is highly expressed in COPD mice and promotes lung injury and inflammation via activation of NLRP3 inflammasome-mediated pyroptosis. Furthermore, inhibition of TREM-1 notably improved the injury in lung tissues of COPD mice and suppressed the activation of NLRP3 inflammasome and pyroptosis, which may provide a novel therapeutic target for COPD treatment.⁷⁹ Some studies found that inhibition of pyroptosis could ameliorate CS-induced COPD.^{80,81} For example, (-)-Epicatechin ameliorated CS-induced lung inflammation via inhibiting ROS/NLRP3 inflammasome-mediated pyroptosis in rats with COPD.⁸⁰ Exosomes derived from adipose-derived stem cells could inhibit alveolar macrophages pyroptosis, thereby attenuated lung injury and inflammation caused by CS.⁸¹

Asthma

Asthma is a common chronic inflammatory airway disease that results from the interaction between inflammatory cells (eg mast cells, eosinophils, neutrophils, and T cells) and inflammatory cytokines.⁸² It is characterized by airway hyper-responsiveness, airway inflammation, airway remodeling, and reversible airflow limitation due to occupational or environmental exposure to microbes, industrial products, and other allergens. In patients with asthma, clumps of epithelial cells in the sputum and increased epithelial cells in bronchoalveolar lavage fluid (BALF) indicate that epithelial cell sloughing is a pathological characteristic of asthma.^{83,84} Furthermore, recent studies have demonstrated pyroptosis in experimental models of asthma and in cell lines.^{20,85–87} Therefore, epithelial cell pyroptosis may represent a pathogenic mechanism contributing to inflammatory injury of airway epithelia. Toluene diisocyanate-induced pyroptosis in bronchial epithelial cells is mediated by the NLRP3 inflammasome, resulting in cytomembrane fracture and release of inflammatory mediators. It is observed in asthmatic mice; it enhances airway sensitivity and responsiveness, and causes continuous airway inflammation. MCC950, a specific NLRP3 inhibitor, can inhibit pyroptosis in bronchial epithelial cells and asthmatic mice and slow the progression of asthma.⁸⁵ Der f1-induced pyroptosis in bronchial epithelial cells through the NLRP3 inflammasome pathway plays a key role in asthma pathogenesis and airway remodeling, and a caspase-1 inhibitor (Z-YVAD-FMK) inhibits the release of IL-1 β and subsequently, Der f1-induced pyroptosis.²⁰ Simultaneously, a new study suggests that *PARK2*, a Parkinson's disease-associated gene that is involved in house dust mite-induced pyroptosis in BEAS-2B cells negatively regulates NLRP3 protein via ubiquitination; therefore, *PARK2* is a negative upstream regulator of the NLRP3 inflammasome.⁸⁶ In addition, a recent study has shown that pyroptosis plays an important role in promoting airway remodeling in the pathogenesis of asthma.⁸⁸

GSDMB is highly expressed in differentiated bronchial epithelial cells, and cleavage of GSDMB by caspase-1 induces pyroptosis. Furthermore, multiple coding variants in the *GSDMB* gene in the 17q21 locus are associated with reduced asthma risk, and the splicing variant, rs11078928, abolishes the pyroptotic activity of GSDMB. This implicates GSDMB-mediated epithelial cell pyroptosis in the pathogenesis of asthma and provides a potential asthma therapy targeting pyroptosis.⁸⁷ These results confirm that targeting inflammasomes and pyroptosis can provide a new direction for the treatment of asthma.

Acute Lung Injury (ALI)/ARDS

ALI/ARDS as acute diffuse pulmonary inflammation is characterized by hypoxemia, diffuse alveolar injury, and acute respiratory failure, leading to an increase in pulmonary microvascular endothelial permeability, pulmonary edema, and the reduction of lung tissue involved in ventilation.⁸⁹ Its high mortality rate has a significant impact on public health.⁹⁰ The inflammasome pathway and its downstream cytokines play critical roles in ARDS development.⁹¹ IL-18 and caspase-1 promote the development of ARDS. Moreover, IL-18 is increased in circulation, which correlates with disease severity and mortality in the MICU.⁹¹ Notably, pyroptosis in alveolar macrophages plays an essential role in the pathogenesis of ALI/ARDS.^{92–94} LPS recognized by TLR4 not only activates the NLRP3 inflammasome and subsequently promotes the release of IL-1 β , but also upregulates IL-1R1 expression on alveolar macrophage surface through the MyD88/NF- κ B dependent pathway. The upregulated expression of IL-1R enables the sensitization of alveolar macrophages to IL-1 β and causes pyroptosis. In summary, the LPS-TLR4 pathway triggers alveolar macrophages and augments ALI/ARDS via secondary upregulation of IL-1 β -IL-1RI signaling.⁹² NLRP3 inflammasome-mediated pyroptosis in macrophages may also play a crucial role in the pathogenesis of ALI/ARDS via the p38 MAPK signal pathway and blocking this pathway can ameliorate ALI by inhibiting macrophage pyroptosis and converting pyroptosis to apoptosis.⁹³ Interestingly, extracellular histones promote alveolar macrophages pyroptosis through the NLRP3/caspase-1 pathway, which in turn aggravates lung inflammation in ARDS.⁹⁴ Phospholipid scramblase 4 (PLSCR4) is a member of single-pass transmembrane proteins that can transfer phospholipids (PS) from the inside to the outside of the cell membrane in a Ca²⁺-dependent manner.⁹⁵ PLSCR4 can reduce the binding of the pyroptosis executive protein GSDMD-NT to PS and the formation of pyroptosis pores, thereby reducing the degree of pyroptosis. Furthermore, PLSCR4 is mainly regulated by P62280.⁹⁵ Recently, Kerr et al have shown that extracellular vesicle-mediated inflammasome and pyroptosis play a role in traumatic brain injury (TBI)-induced ALI model in mice and patients, and ASC can be used as an excellent biomarker for the diagnosis of TBI-induced ALI. In addition, anti-ASC treatment significantly reduces inflammasome activation and TBI-induced ALI.^{96,97} Therefore, these studies provide new therapeutic strategies for controlling ALI/ARDS. Interestingly, NecroX-5, an inhibitor of necrosis, alleviated lung inflammation in murine models with ALI/ARDS by inhibiting the NF- κ B signaling pathway and inhibiting activation of the NLRP3 inflammasome. We speculate that there is crosstalk between necrosis and pyroptosis.⁹⁸ Therefore, a comprehensive investigation of pyroptosis and its correlation with other cell death pathways would provide a novel therapeutic strategy for the treatment of ARDS.

Pulmonary Fibrosis

Pulmonary fibrosis is characterized by progressive and irreversible destruction of the lungs, leading to progressive decline in lung function. The mechanism underlying pulmonary fibrosis is not yet fully understood. Asbestosis, silica, CS, particulate matter, and bleomycin (BLM) are associated with pulmonary fibrosis.⁹⁹ Many studies indicate that inflammasomes, such as the NLRP3 and AIM2 inflammasomes, which are tightly associated with pyroptosis, play critical roles in the pathogenesis of pulmonary fibrosis. Several published studies have shown that the NLRP3 inflammasome is involved in lung fibrosis in both experimental models and patients. The NLRP3 inflammasome promotes the release of IL-1 β , which can promote fibroblast-to-myofibroblast differentiation and activate the TGF- β 1/Smads signal pathway.^{100–103} NLRP3 inflammasome activation in alveolar epithelial cells promotes myofibroblast differentiation of lung-resident mesenchymal stem cells, and MCC950 attenuates BLM-induced pulmonary fibrosis.¹⁰⁴ Moreover, a study has confirmed that NLRP3 inflammasome activation in aged mice increases susceptibility to pulmonary fibrosis.¹⁰³ AIM2 inflammasome activation has been found in peripheral blood mononuclear cells (PBMCs) from patients with idiopathic pulmonary fibrosis (IPF), which leads to the activation of caspase-4, which induces the release of IL-1 α responsible for the release of transforming growth factor beta 1 (TGF- β 1) from PBMCs.¹⁰⁵ Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) participates in the destruction of lysosomes and promotes the production of ROS. ROS production and cathepsin B are directly involved in NLRP3 inflammasome activation. Moreover, N-acetyl-L-cysteine can attenuate NLRP3 inflammasome activation and lung fibrosis.¹⁰⁶ Treatment targeting NLRP3, AIM2, caspase-1, IL-1 β , and ROS can effectively alleviate pulmonary fibrosis, which may also serve to inhibit lung injury and fibrosis. Another study found that the activation of NLRP3 inflammasome was impaired in patients with IPF, and the level of IL-18 in the BALF was lower than that in control patients. This may be because the innate immune response of patients with IPF is impaired, including

reduced function of macrophages to kill pathogenic bacteria.¹⁰⁷ While the NLRP3 inflammasome was activated, the levels of NLRP3 and caspase-1 were increased in patients with RA-UIP, and IL-1 β and IL-18 were significantly elevated in the BALF and BALF macrophages.¹⁰⁷ Autophagy and NLRP3 inflammasomes are activated in patients with fibrosis and are positively correlated with oxidation in vivo.¹⁰⁸ Angiotensin-II (Ang II) promotes intercellular ROS and NOX4 levels, leading to NLRP3 inflammasome activation and stimulates collagen synthesis through the NLRP3/caspase-1/IL-1 β pathway. Furthermore, autophagy suppresses NLRP3 inflammasome activation by eliminating ROS and alleviating mitochondrial dysfunction. Taken together, autophagy alleviates pulmonary fibrosis by regulating NLRP3 inflammasome activation induced by Ang II-mediated via redox balance modulation.¹⁰⁸ NLRP3 inflammasome-mediated pyroptosis in macrophages promotes collagen synthesis and the progression of pulmonary fibrosis in BLM-induced pulmonary fibrosis models, and lycorine ameliorates pulmonary fibrosis by inhibiting the NLRP3 inflammasome and pyroptosis.²⁴ Another study reported that bone marrow-derived mesenchymal stem cells can inhibit pyroptosis triggered by NLRP3/caspase-1 in silica-induced pulmonary fibrosis.¹⁰⁹ Emerging studies have shown that AIM2 inflammasome activation and pyroptosis in macrophages are involved in the pathogenesis of radiation-induced pulmonary fibrosis. Andrographolide ameliorated radiation-induced pulmonary fibrosis by inhibiting AIM2 inflammasome-mediated pyroptosis in macrophages, thus, identifying andrographolide as a new potential protective agent against for radiation-induced pulmonary fibrosis.¹¹⁰ These studies demonstrated that inflammasomes and induced pyroptosis participate in the pathogenesis of pulmonary fibrosis, and would provide new targets for patients with pulmonary fibrosis.

Pulmonary Infection

Macrophage pyroptosis is a protective mechanism against *Klebsiella pneumoniae* infection and facilitates the clearance of bacteria.^{111,112} Pyroptosis mediated by caspase-11 can promote neutrophil recruitment and bacterial clearance against *K. pneumoniae* infection, and caspase-11 knockout blocks this effect.¹¹² However, different clinical strains of *K. pneumoniae* have different mechanisms of survival within macrophages. The A28006 strain induced macrophage pyroptosis and high IL-1 β production, which is easily cleared; in contrast, the A54970 strain induced high IL-10 production, which inhibited macrophage pyroptosis to evade host defense, resulting in the dissemination of bacteria.¹¹¹ Studies on *Salmonella typhimurium* and *Legionella pneumophila* have revealed that bacteria flagellin is an agonist of NLRC4 inflammasome-mediated pyroptosis in macrophages, which restricts bacterial replication in vivo. However, *Salmonella typhimurium* avoids innate immune mechanisms by evading NLRC4 inflammasome-mediated pyroptosis.^{113,114} NLRC4 inflammasome-mediated pyroptosis plays a protective role during *Burkholderia pseudomallei* infection. Knockdown of NLRC4 in mice causes high susceptibility to bacterial infections due to reduced pyroptosis and an increased bacterial burden. Moreover, IL-18 cleaved by the NLRP3 inflammasome protects against *B. pseudomallei* lung infection, due to its ability to increase the production of interferon (IFN- γ), whereas IL-1 β is deleterious because of excessive recruitment of neutrophils to the lung.¹¹⁵ Wang et al analyzed the protective role of the canonical and noncanonical pyroptosis pathways during *B. pseudomallei* infection. Caspase-1 triggers pyroptosis, mainly in infected macrophages, and controls the release of IL-18. In contrast, caspase-11-mediated pyroptosis mainly occurs in infected lung epithelial cells.¹¹⁶ In summary, pyroptosis is an efficient effector mechanism that restricts bacterial growth and dissemination during *B. pseudomallei* infection. NLRC4 inflammasome-mediated pyroptosis plays different roles during *Pseudomonas aeruginosa* infection, depending on host conditions. Flagella-expressing *P. aeruginosa* can activate the NLRC4 inflammasome and promote the secretion of IL-1 β /IL-18 by macrophages in acute *P. aeruginosa* pneumonia, and NLRC4 inflammasome signaling not only impairs bacterial clearance but is also involved in increased mortality. Strategies limiting NLRC4 inflammasome activation have limited the pathological consequences of acute *P. aeruginosa* pulmonary infection.¹¹⁷ However, NLRC4 inflammasome is failed to activate by clinical isolates of *P. aeruginosa* from chronically infected cystic fibrosis patients during both stable and exacerbation infection, which indicated that *P. aeruginosa*-activated inflammasomes are not involved in cystic fibrosis pulmonary exacerbations.¹¹⁸ Emerging evidence revealed that neutrophils pyroptosis were essential for host protection during *P. aeruginosa* lung infection in the absence of NOX2.¹¹⁹ Thus, specifically target neutrophil pyroptosis are likely to be useful for curing highly intractable *P. aeruginosa* infections. *Acinetobacter baumannii*-induced pyroptosis contributes to the lung damage and high mortality in a

pneumonia mouse model. Interestingly, caspase-1/11 knockout played a protective role in mice infected with *A. baumannii*. The hLF (1-11) peptide improves the survival of *A. baumannii* pneumonia in mice by inhibiting caspase-1-mediated pyroptosis.¹²⁰ Another study claimed that *A. baumannii* infection induces the activation of multiple cell death pathways, such as pyroptosis and necrosis, and that type I IFN exerts a protective effect against *A. baumannii* infection by regulating histone modifications.¹²¹ GSDME-mediated pyroptosis plays a lethal role in H7N9 virus infection; knockdown of GSDME switched lung epithelial cell pyroptosis to apoptosis upon H7N9 virus infection, and protected mice from an H7N9 virus lethal infection.¹²² Therefore, specifically targeting GSDME-mediated pyroptosis is a potential therapeutic approach for H7N9 virus infection. Therefore, pyroptosis plays a crucial role as a positive or negative regulator in the pathogenesis of pulmonary infection. It is a potential therapeutic strategy for pulmonary infection, even in multi-drug-resistant bacterial infections.

Lung Cancer

Lung cancer is the most common cancer and leading cause of cancer-related mortality worldwide. GSDMD expression was increased in non-small cell lung cancer (NSCLC) and was associated with tumor metastasis.¹²³ Moreover, high GSDMD expression implies a poor prognosis in lung adenocarcinoma but not in squamous cell carcinoma.¹²³ GSDMD knockdown alleviated tumor proliferation by switching NLRP3/caspase-1-mediated-pyroptosis to apoptosis and suppressing the epidermal growth factor receptor/protein kinase pathway in NSCLC.¹²³ Therefore, GSDMD may be used as an independent prognostic biomarker for lung adenocarcinoma. Furthermore, GSDMD plays an essential role in tumor immunity through GSDMD, contributing to cytotoxic T lymphocyte-mediated killing.¹²⁴ Emerging evidence has revealed that caspase-3/GSDME-mediated pyroptosis is involved in the treatment of NSCLC with chemotherapy.^{58,125–127} Paclitaxel and cisplatin, as representative chemotherapeutic drugs for lung cancer, could induce apoptosis in A549 cells, but caspase-3/GSDME-induced pyroptosis was observed in some dying cells. Furthermore, cisplatin induced higher levels of pyroptosis in A549 cells than paclitaxel did, and GSDME knockdown significantly inhibited cisplatin-induced pyroptosis, which revealed that cisplatin may provide additional advantages in the treatment of lung cancers with high levels of GSDME expression.¹²⁵ Another study explored the effect of GSDME-mediated pyroptosis in the treatment of NSCLC with cisplatin and claimed that GSDME-mediated pyroptosis enhances cisplatin sensitivity to NSCLC, and low GSDME expression in tumor tissues indicates a short survival time and high mortality rate after platinum treatment.¹²⁶ GSDME-mediated pyroptosis promoted tumor CD3+T cell infiltration via GSDME-NT pores.¹²⁶ GSDME is silenced in most cancer cells due to methylation of the *GSDME* gene. The combination of methylation inhibitors and chemotherapy agents can convert apoptosis into caspase-3/GSDME-mediated pyroptosis and significantly improve the efficacy of chemotherapy through immune activation by pyroptosis.¹²⁷ Therefore, GSDME-mediated pyroptosis may be conducive to improve the chemotherapy sensitivity of lung cancer and may provide a new potential target for the development of lung cancer immunotherapy. miR-556-5p is a small non-coding RNA that is significantly upregulated in patients with cisplatin-resistant NSCLC.¹²⁸ Silencing of miR-556-5p enhances the sensitivity of cisplatin by inducing NLRP3-mediated pyroptosis in cisplatin-resistance NSCLC cells.¹²⁸ Long non-coding RNA X-inactive specific transcript (lncRNA-XIST) is an oncogene in various cancers and is aberrantly overexpressed in NSCLC tissues or cell lines, which promotes NSCLC cell proliferation, invasion, and metastasis.^{129,130} Downregulation of lncRNA-XIST can promote ROS production and NLRP3 inflammasome activation to induce pyroptosis.^{129,130} Moreover, miR335 is the downstream target of lncRNA-XIST, and lncRNA-XIST regulates superoxide dismutase 2 (SOD2) levels by targeting miR-335. Taken together, knockdown of lncRNA-XIST suppressed NSCLC development by inducing miR-335/SOD2/ROS-mediated pyroptosis.¹²⁹ Xu et al revealed that lncRNA-XIST was upregulated in NSCLC cells previously treated with cisplatin. Interestingly, knockdown of lncRNA-XIST promoted chemosensitivity to cisplatin by inducing pyroptosis in NSCLC cells.¹³⁰ Taken together, these findings reveal that pyroptosis may participate in the regulation of chemotherapeutic sensitivity in NSCLC, which provides new therapeutic strategies to overcome chemo-resistance in patients with NSCLC in clinical setting. Additional studies have found that triggering pyroptosis is a novel approach for treating lung cancer. For instance, cucurbitacin B inhibited NSCLC in vivo and in vitro by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis, which supports cucurbitacin B as a potential therapeutic agent for NSCLC.¹³¹ Simvastatin inhibited proliferation and metastasis in NSCLC via pyroptosis mediated by the NLRP3/caspase-1 pathway.¹³² Polyphyllin VI (PPVI) activated the NLRP3 inflammasome and induced the apoptosis-to-

pyroptosis switch in NSCLC, which supported that PPVI might be a new candidate for the future treatment of NSCLC.¹³³ L61H10, a heterocyclic ketone derivative exerted anti-tumor effects in NSCLC, mainly through the switch of apoptosis-to-pyroptosis mediated by the NF- κ B signaling pathway.¹³⁴

Inhibitors of Pyroptosis

In recent years, great progress has been made in research on the molecules involved in the process of pyroptosis. Herein, we provide a brief introduction to the therapeutic strategies for the inhibition of pyroptosis (Table 1).

Inhibitors of Proinflammatory Caspases

IDN-6556, VX-740 (pralnacasan), and its analog VX-765 are common caspase-1 Inhibitors.¹³⁵ VX-740 and VX-765 are peptidomimetic drugs, which both catalyze the active site cysteine residues of caspase-1 by reversible covalent attack. IDN-6556 acts through irreversible covalent modification of catalyzing the active site cysteine residues, thus inhibiting caspase-1 and reducing the release of IL-1 β /IL-18.^{34,135} VX-765 and VX-740 were effective in the treatment of RA and osteoarthritis in murine models, and they blocked the release of IL-1 β and IL-18.^{136,137} Furthermore, VX765 reversed cognitive impairment and neuroinflammation in mouse models of AD.¹³⁸ It reduces the area of myocardial infarction and maintains ventricular function in mice models.¹³⁹ To date, three caspase-1 inhibitors (VX-740, VX-765 and IDN-6556) have entered clinical trials for RA, epilepsy, psoriasis, and chronic hepatitis C viral infection; however, IDN-6556 has been withdrawn from clinical trials because of undisclosed reasons.^{140–142} VX-765 was reported to alleviate airway inflammation in the mice models with asthma,²¹ and rescued the degree of emphysema in CS-exposed mice.⁷⁸

NLRP3 Inflammasome Inhibitors

MCC950, a diarylsulfonylurea-containing compound, is the best-studied NLRP3 inhibitor; it is highly specific and selective. It inhibits NLRP3 inflammasome activation and IL-1 β production by blocking ASC oligomerization, which is specific for the NLRP3 inflammasome, and does not affect the activation of other inflammasomes.¹⁴³ A recent study

Table 1 Inhibitors of Pyroptosis and Their Targets

Agents	Target(s)	Potential Mechanism	References
VX-740 VX-765	Caspase-1	Reversible covalent attack of catalyzing the active site cysteine residues of caspase-1 resulting in inhibiting caspase-1 and the release of IL-1 β /IL-18	[136,137]
IDN-6556	Caspase-1	Irreversible covalent modification of catalyzing the active site cysteine residues of caspase-1 blocking in inhibiting caspase-1 and the release of IL-1 β /IL-18	[34,135]
MCC950	NLRP3 (directly)	Directly interact with the NACHT domain and block ATP hydrolysis resulted in blocking the canonical and non-canonical NLRP3 inflammasome activation	[143,144]
Glyburide	NLRP3 (indirectly)	Act downstream of P2X7 inhibiting the aggregation of ASC	[145]
ICI100	ASC	Prevent ASC oligomerization and prevent recruitment of ASC into the inflammasome complex	[146]
Punicalagin	GSDMD	Block plasma membrane fluidity and interfere with correct GSDMD-NT insertion into the cell membrane	[148]
Necrosulfonamide	GSDMD	Directly binding to GSDMD through Cys191 and inhibits the formation of pores via GSDMD-NT fragments on the plasma membrane	[150]
LDC7559	GSDMD	Remain unknown	[56]
DMF	GSDMD, GSDME	DMF reacts with GSDMD and GSDME at critical cysteine residues to form S-(2-succinyl)-cysteine, thereby inhibits pyroptosis.	[151]
Disulfiram	GSDMD	Disulfiram covalently modifies human Cys191/mouse Cys192 in GSDMD to block pore formation of GSDMD	[152]

revealed that MCC950 directly interacts with the NACHT domain and blocks ATP hydrolysis and can rescue airway remodeling and alleviate neutrophil airway inflammation in asthma murine models.^{21,144} Another study reported that MCC950 inhibits pyroptosis in human bronchial epithelial cells mediated by the NLRP3 inflammasome.⁸⁵

Glyburide, a sulfonylurea drug, has recently been found to indirectly inhibit the activation of the NLRP3 inflammasome. Research has shown that glyburide inhibits PAMPs and DAMPs induced by NLRP3 inflammasome activation, while inhibiting the activation of caspase-1 and secretion of IL-1 β , which acts downstream of P2X7, inhibiting the aggregation of ASC.¹⁴⁵

IC100, a monoclonal antibody targeting ASC, acts extracellularly to prevent ASC oligomerization and recruitment into the inflammasome complex.¹⁴⁶ A study found that IC100 inhibits the immune inflammatory response that drives the development and progression of experimental autoimmune encephalomyelitis.¹⁴⁶ Anti-ASC treatment significantly suppresses inflammasome activation and TBI-induced ALI.^{96,97}

Gasdermin Inhibitors

Punicalagin was the first compound to block pyroptosis and IL-1 β release.^{147,148} Punicalagin blocks plasma membrane fluidity and interferes with correct GSDMD-NT insertion into the cell membrane.¹⁴⁸ Moreover, a recent study suggested that punicalagin affects the activation of NLRC4 and NLRP1 inflammasomes, possibly by affecting membrane fluidity and blocking the delivery of inflammasome activators.¹⁴⁹ In contrast, punicalagin has no effect on the generation of GSDMD-NT and activation of NLRP3 and AIM2 inflammasome.¹⁴⁸

Necrosulfonamide is a cysteine-reactive drug that inhibits pyroptosis in murine macrophages and human monocytes.¹⁵⁰ It directly binds to GSDMD through Cys191 and inhibits the formation of pores via GSDMD-NT fragments, thereby inhibiting the release of IL-1 β . Necrosulfonamide is highly specific for GSDMD and has no effect on inflammasome activation and pyroptosis induced by the GSDME-NT terminal.¹⁵⁰

LDC7559, a NET formation inhibitor based on the pyrazolo-oxazepane scaffold, binds to GSDMD and blocks neutrophil elastase-dependent pyroptosis in human neutrophils; however, its mechanism is unclear.⁵⁶

Dimethyl fumarate (DMF) is an intermediate in the citric acid cycle, and is currently used in the treatment of multiple sclerosis. DMF reacts with GSDMD at critical cysteine residues to form S-(2-succinyl)-cysteine. GSDMD succination prevents activation of inflammatory caspases and inhibits pyroptosis. DMF protects against familial Mediterranean fever and experimental autoimmune encephalitis in mice by inhibiting pyroptosis.¹⁵¹ Furthermore, DMF inhibits GSDME-mediated pyroptosis through GSDME succination.¹⁵¹

Disulfiram, an inhibitor of acetaldehyde dehydrogenase, has been approved for the treatment of alcohol addiction. A recent study revealed that disulfiram covalently modified human Cys191/mouse Cys192 in GSDMD to block pore formation of GSDMD. Interestingly, disulfiram had no effect on the processing of GSDMD and IL-1 β but abrogates GSDMD pore-formation.¹⁵²

Potential Medicines for Pyroptosis in Respiratory Diseases

Cucurbitacin B is a natural triterpenoid derived from *Cucurbitaceae* plants. A previous study found that cucurbitacin B could directly interact with TLR4 to activate the NLRP3 inflammasome and increase mitochondrial ROS production to induce pyroptosis, subsequently inhibiting NSCLC in vivo and in vitro.¹³¹ Simvastatin, the most commonly used statin, can suppress proliferation and migration in NSCLC through caspase-1-mediated pyroptosis.¹³² PPVI, as the main saponin in *Trillium tschonoskii* Maxim, could activate the NF- κ B pathway by increasing the generation of ROS, thereby activating the NLRP3 inflammasome. Moreover, PPVI induced an apoptosis-to-pyroptosis switch. Taken together, PPVI could inhibit the progression of NSCLC via pyroptosis.¹³³ L61H10 is a heterocyclic ketone derivative, that exerts antitumor effects in NSCLC. L61H10 inhibited NF- κ B signaling pathway and induced apoptosis-to-pyroptosis switch to exert anti-tumor effect.¹³⁴ Andrographolide, an active component extracted and purified from *Andrographis paniculata*, which alleviated radiation-induced lung injury by inhibiting AIM2 inflammasome-mediated pyroptosis in macrophages.¹¹⁰ Resveratrol could suppress autophagic process and NLRP3 inflammasome activation, thereby alleviated particulate matter-induced lung inflammation and fibrosis.¹⁵³ Lycorine could inhibit NLRP3 inflammasome and pyroptosis by targeting ASC pyrin domain, which exerted anti-fibrotic effect in BLM-induced pulmonary fibrosis.²⁴ Scutellarin and Fluorofenidone attenuated

pulmonary fibrosis via inhibiting NLRP3 inflammasome and NF- κ B signaling pathway.^{154,155} NAC also alleviated pulmonary fibrosis by inhibiting the activation of NLRP3 inflammasome, but clinical trials have confirmed that it has no significant effect on IPF.¹⁰⁶ Luteolin could regulate the frequency of Tregs and the levels of Treg derived IL-10, which suppressed pyroptosis mediated by caspase-11 in sepsis-induced ALI, thereby alleviated lung injury.¹⁵⁶ -Epicatechin (EC), a type of flavonoid, which promoted ubiquitin-mediated Keap1 degradation by upregulating tripartite motif-containing protein 25 expression and enhanced the nuclear localization of Nrf2 protein. Moreover, EC notably inhibited the NLRP3 inflammasome and pyroptosis. Therefore, EC ameliorated cigarette smoke-induced lung inflammation by inhibiting ROS/NLRP3 inflammasome pathway in rats with COPD.⁸⁰

Conclusions

In summary, pyroptosis is a new type of cell death and the executor is the gasdermin family, which is mainly regulated by the caspase-1-mediated canonical and the caspase-4/5/11-mediated noncanonical pathways. The occurrence and progression of pulmonary diseases are related to pyroptosis, and the NLRP3 inflammasome is the most well-studied mechanism. This review highlighted the significance of pyroptosis in the pathogenesis of COPD, asthma, ALI/ARDS, pulmonary fibrosis, lung cancer, and pulmonary infection. The role of pyroptosis as a key target for the treatment of pulmonary diseases has also been highlighted. In addition, we illustrated potential drugs that may become possible therapeutic targets for the management and treatment of respiratory diseases. These studies have revealed that targeting pyroptosis and inflammasomes also plays a role in the treatment of respiratory diseases, providing new ideas for the treatment of respiratory diseases.

At present, the study of pyroptosis is still in its infancy, and many mechanisms are still unclear. For instance, caspase-3/8 play an important role in apoptosis, but recent studies have shown that it is also involved in the process of pyroptosis. Therefore, when and what conditions does the transition between pyroptosis and apoptosis occur? Is pyroptosis an independent mode of cell death, or is it accompanied by other modes of cell death? In addition, there is crosstalk between pyroptosis and necroptosis, what is the mechanism? Such questions still need to be proven by a great deal of studies.

Several agents regulate the pyroptosis pathway. However, studies have largely focused on cancer treatment and autoimmune diseases. Research and development of medicines for the treatment of pulmonary diseases is ongoing. In the future, medicines targeting pyroptosis could be used to treat lung-related diseases. This will provide a better direction for the development of medications for pulmonary-related diseases.

Abbreviations

AIM2, absent in melanoma; ALI, acute lung injury; Ang II, angiotensin; ARDS, acute respiratory distress syndrome; ASC, apoptosis-associated speck like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; BALF, bronchoalveolar lavage fluid; BLM, bleomycin; CARD, caspase recruitment domain; COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; DAMPs, damage-associated molecular patterns; Der f1, Dermatophagoides farina 1; DMF, dimethyl fumarate; GSDMD, gasdermin D; GSDMD-CT, GSDMD C-terminal; GSDMD-NT, GSDMD N-terminal; HMGB1, high mobility group box 1; IFN, interferon; IL, interleukin; IPF, idiopathic pulmonary fibrosis; LncRNA-XIST, long non-coding RNA X-inactive specific transcript; LPS, lipopolysaccharide; LRR, leucine-rich repeat; MyD88, myeloid differentiation primary response 88; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NF- κ B, nuclear factor kappa B; NLR, nucleotide-binding oligomerization domain-like receptor; NLRC, NLR family CARD containing proteins; NLRP3, NLR family pyrin domain containing proteins; NOD, nucleotide-binding oligomerization domain; NOX, NADPH oxidase; NSCLC, non-small cell lung cancer; PAMPs, pathogen-associated molecular patterns; PBMCs, peripheral blood mononuclear cells; PRRs, pattern recognition receptors; PYD, pyrin domain; RA-UIP, rheumatoid arthritis-associated-usual interstitial pneumonia; ROS, reactive oxygen species; TBI, traumatic brain injury; TGF- β 1, transforming growth factor beta 1; TNF- α , tumor necrosis factor alpha; TLR, Toll-like receptor; TREM-1, triggering receptor expressed on myeloid cells; TXNIP, thioredoxin-interacting protein; MAPK, mitogen-activated protein kinase; PLSCR4, Phospholipid scramblase 4; PS, phospholipids.

Author Contributions

TYS and JLL designed the entire subject. JLL, GQF, and NNT: literature collection. YYS and JLL wrote the article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work

Disclosure

The authors report no conflicts of interest in this work.

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