REVIEW

Pyroptosis and Airway Homeostasis Regulation

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Summary

Pyroptosis is a form of cell death associated with inflammation. In the maintenance of airway homeostasis, pyroptosis goes through activation and assembly of Inflammasome. The pyroptosis pathway is mediated by caspase which activates the pore-forming effect of substrate gasdermin family members. It eventually leads to lysis and release of the cell contents and then induces an inflammatory response. In this process, it participates in airway homeostasis regulation by affecting airway immunity, airway epithelial structure and airway microbiota. Therefore, we discussed the correlation between airway immunity, airway epithelial structure, airway microbiota and the mechanism of pyroptosis to describe the role of pyroptosis in airway homeostasis regulation which is of great significance for understanding the occurrence and treatment of airway inflammatory diseases.

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Introduction

Pyroptosis plays an important role in regulating the organism's life activities. During the transition from defining cell death in terms of morphological characteristics to defining cell death in terms of molecular signaling pathways, people defined cell death has expanded from the original simple description regulating cell death to cellular senescence, autophagy-dependent cell death, mitotic catastrophe, entotic cell death, ferroptosis, immunogenic cell death, lysosome dependent cell death, and mitochondrial permeability transition (MPT)-driven necrosis etc. [1]. Among them, pyroptosis described in this review refers to the release of a large number of inflammatory mediators when cells die. Chronic airway inflammation and respiratory tract infection have been important public health problems. Pyroptosis has been found to be associated with many diseases, but the relationship between pyroptosis and airway diseases is still little studied.

Mechanism of pyroptosis involved in airway injury

In the study of pyroptosis, two types of pyroptosis pathways have been found, one is the classical pathway dependent on caspase-1 dominance, and the other is the non-classical pathway dependent on caspase-4, -5 and -11 dominance. When the airway senses the danger signal, it will stimulate the natural immunity and activate the caspase-dependent signaling

pathway through the assembly of inflammasome to induce the formation of Gasdermin holes. This process will lead to the rupture of cell membrane which will induce the inflammatory response of the body. Therefore, pyroptosis can be understood as a double-edged sword. A certain degree of pyroptosis can help the body recognize danger signals, prevent the invasion of infectious pathogens and play a protective role in the body. However, when the body is beyond the tolerance, inflammation will be induced. Such as cytokine release syndrome, sepsis, chronic obstructive pulmonary disease, inflammatory bowel disease, tumor, etc. [2-5]. Therefore, how to overcome excessive inflammatory activities caused by pyroptosis has formed many ideas for researchers to treat diseases (Table 1).

Table 1. Ideas for the treatment of pyroptosis.

Mechanism of way	Object	Drug Research	Reference
NLRP3 inhibitors	Rodent model	Flufenac acid, methlofenac acid, mefenac acid and other non-steroidal anti-inflammatory drugs	[6]
Inhibition of pyroptosis by targeting TLR2 and NF-κB1	Human with type 2 diabetes	Butyrate	[7]
NLRP3 inhibitors	Mice	Tranilast	[8]
Block gasdermin D hole	Human, Mice	Disulfiram	[9]
Gasdermin C activator	Mice	PDL-1 inhibitors	[10]
NLRP3 inhibitors	Mice	Vinyl sulfones	[11]
NLRP3 inhibitors	Rodent	Taurine	[12]
Inhibits NLRP3, Caspase-1, GSDMD, IL-1β and IL-18	Human	Atorvastatin	[13]
Inhibit caspase-1, IL-1β and IL-18	Human	Rapamycin	[14]

Triggering of pyroptosis – inflammasome formation

In the damage mechanism that balances airway homeostasis, the innate immune cells that initiate the first attack recognize pathogen-associated molecular pattern (PAMP) and damage-related molecular pattern (DAMP) through pattern recognition receptor (PRR). Then they assemble into complex composed of multiple proteins through cascade signals, namely inflammasome. Among them, PAMP mainly recognizes lipopolysaccharide, lipoprotein, carbohydrate, nucleic acid and flagellin, so that the host can sense a wide range of pathogenic microorganisms [15]. Intracytoplasmic PRR activates inflammasome in combination with apoptosis-associated spotted protein (ASC) and pro-caspase-1 precursor. So far, the discovered PRR family includes Toll receptor (TLR) and C-type lectin receptor (CLR) in plasma membrane and endosomes, as well as RIG-I like receptor (RLR), AIM 2-like receptor (ALR) and NOD-like receptor (NLR) in cells [6]. ALR and NLR are the main families which are involved in inflammasome assembly.

The NLR family consists of N-terminal domain, central domain required for oligomerization (NOD) and C-terminal domain that binds ligands and sensing signals with leucine-rich repeat sequences (LRR). We have identified inflammasomes such as NLRP3, NLRC4, AIM2, NLRP1, Pyrin, etc., but the inflammasome we have studied most intensively is NLRP3.

Activation of inflammasome

Activation of inflammasome begins with the recognition of specific signal stimuli by NLR, ALR, etc. The first signal stimulation refers to the activation of bone marrow differentiation factor (MyD88) after pathogen stimulation which mediates phosphorylation and degradation of IkB, activates nuclear factor-κB (NF-κB) to trigger a cascade reaction [16]. The second signal is a wide range of stimuli such as urate crystals, heparin sulfate, nanoparticles, silica, asbestos, pore-forming toxins, extracellular ATP, crystals, etc., they can alter cell homeostasis and trigger a cascade reaction. The third signal is the rapid response of bone marrow derived macrophages (BMDM) by lipopolysaccharide (LPS) of

Gram-negative bacteria, independent of ATP, which internizes and activates the non-classical pathway, triggering the activation of NLRP3 inflammasome and rapid response of the body to bacteria from the side

Assembly of inflammasome

NLRP3 consists of three parts: Pyrin domain (PYD), NATCH core domain and LRR domain. When the LRR domain senses the signal, it activates the core domain NATCH to promote the oligomerization of NLRP3 and expose the amino terminal PYD. It is assembled in the trans-Golgi network with ASC and pro-Caspase-1 proteins. ASC was originally found in leukemia cells and can be expressed at high levels in a variety of macrophages. ASC exists as a soluble protein in the cytoplasm and nucleus of unstimulated cells and ASC acts as an important junction protein. When the body's inflammasome starts to activate, ASC can quickly assemble. On the one hand, pro-caspase-1 is recruited and its hydrolysis and activation is induced; on the other hand, ASC aggregates to form the activation platform of Caspase-1 and eventually forms spot-like complexes. The formation process is synergically regulated by phosphorylation, ubiquitination and ion channels.

Inflammatory bodies activate caspase

Caspase activation begins after activation and assembly of NLRP3 inflammasome components. This process is controlled by REDOX and changes in REDOX microenvironment can regulate the activation potential of inflammasome [17]. Caspase is a family of cysteine-dependent endonuclease proteases. Structurally, the C-terminal of caspase is the Caspase domain which can hydrolyze the target protein, the N-terminal is the non-enzyme domain, namely death effect domain (DED) and caspase recruitment domain (CARD) which can promote recruitment and aggregation of caspase in the multi-protein complex. Up to now, caspase-2, -3, -6, -7, -8, -9, -10 of the apoptosis family and caspase-1, -4, -5, -11, -12, -14 of the inflammatory family are mainly recognized [18]. The researchers have found that inflammatory caspase-1 can distinguish toxic bacteria from non-toxic bacteria and alert the immune system to the infection of pathogens. Caspase-1 can mediate the lysis of cell solute protein Gasdermin D (GSDMD) to promote the formation of membrane pores and cell lysis [19]. Inflammatory caspase-1 is recruited into the inflammasome through its amino-terminal recruitment

domain CARD which promotes homodimerization and drives autoactivation, assembling the inflammasome that binds to Caspase-1. The hinge regions of n-terminal and C-terminal domains of substrate GSDMD and pro-IL-1β, Pro-IL-18 were directly cut, the lethal fragments of GSDMD were released [20]. Not only caspase-1 has inflammatory properties to cut substrates, but other members of the inflammatory family can also cut GSDMD to induce pyroptosis. Unlike Caspase-1, they can't cut Pro-IL-1β, Pro-IL-18. However, non-classical human caspase-4, -5 or mouse caspase-11 can directly detect the cell solute LPS from Gram-negative bacteria to initiate protein hydrolysis and drive autoactivation, thereby cracking substrate GSDMD [21]. This process also requires the activation of Caspase by the interaction of the recruitment domain CARD with LPS of Gram-negative bacteria. In addition, caspase-8 has been proved to play an important role in inflammasome activation, and Caspase-3, -7 can act as executioners upstream of inflammasome activation [22]. The researchers have found that caspase-11-induced substrate cleavage can promote the release of IL-1β and IL-18 *via* the NLRP3 platform in the classical caspase-1 pathway [23]. This process proves that different pyroptosis pathways are not completely separated.

It is noteworthy that the pyroptosis studied by us does not exist independently from other deaths. Perhaps we can reversibly modulate pyroptosis by affecting other forms of death. When discussing the importance of Caspase family on cell pyroptosis, it is found that pyroptosis and apoptosis pathways have cross-influence. Such as: Caspase-3, the executioner of apoptosis, can cut GSDMD and form a short N-terminal fragment, but it cannot form holes in the membrane, thus preventing the occurrence of pyroptosis; In the absence of GSDMD, the pyroptosis signal can also stimulate caspase-1-mediated apoptosis and the activated Caspase-8 can shear and activate GSDMD · it can induce pyroptosis and inhibit ripk3-mediated cell necrosis pathway, thereby promoting apoptosis [1,21]; Adrenomedullin (ADM) can attenuate pyroptosis in Leydig cells exposed to LPS by promoting autophagy through the ROS-AMPK-mTOR axis [24].

The substrate of GSDMD performs pyroptosis in plasma membrane pore formation

As the only substrate of caspase, GSDMD is involved in the key effector of cell pyroptosis. The activated GSDMD releases N-terminal fragments through

oligomerization and translocation into the cell membrane to form holes which lead to the release of cell contents and the release of inflammatory cytokines triggering downstream responses. Some studies have found that the survival rate of sepsis mice with GSDMD knockout is increased, suggesting that GSDMD inhibitors can provide therapeutic ideas for patients with sepsis. At present, members of gasdermin family known to us include GSDMA, GSDMB, GSDMC, GSDMD, GSDME (DFNA5) and PJVK (DFNB59), etc. The structure of GSDMD consists of an amino terminal domain capable of pore formation and a carboxyl terminal domain capable of pore formation inhibition which are connected through the central joint region. Caspase lyses gasdermin D in the junction region and releases pore forming amino-terminal domain fragments from the carboxy-terminal domain. This segment can penetrate complex liposomes, combine with phospholipids of lobules and mitochondria in the plasma membrane, insert into the plasma membrane at a lower order of magnitude and assemble pores through oligomerization in the membrane guide the formation of a higher number of terminal holes. Finally, the osmotic pressure of the cells changes and the cells swell and lysis. In addition, GSDMD is not the only one associated with pyroptosis. Researchers have found that GSDME can target Caspase-3 and inhibit its binding to apoptotic substrates which can transform apoptotic cells with high expression of GSDME into pyrodeath cells [25]. GSDMB can enhance the activity of Caspase-4 to cut GSDMD. GSDMC can also be transformed into pyroptosis *via* caspase-8 mediated apoptosis.

During this process, mitochondria and other organelles would be damaged. Researchers have found that mitochondrial depolarization was eliminated in the pyroptosis of macrophages that were knocked out of GSDMD, it shows that GSDMD may also target organelles in the inner membrane of cells in addition to destroying plasma membrane [26]. During pyroptosis of the host cell, on the one hand, the pathogen is released out of the cell and killed by neutrophils and so on. On the other hand, pathogens are trapped in scorched corpses to prevent their spread, this is a phenomenon called pore-induced intracellular traps (PIT) and then facilitate clearance by neutrophils and other specialized phagocytes. GSDMD not only plays a role in the change and infiltration of plasma membrane, but also allows non-selective ion flows such as potassium ions and calcium ions to pass through the pore after the formation of the pore. The influx of calcium ions outside the plasma membrane leads to the activation of calprotease, thereby controlling the release of IL-1α. It has been found that phosphatidylinositol feedback regulation of GSDMD dynamics reversibly controls pore function which in turn controls the release of inflammatory cytokines [27]. In response to caspase-4, -5, -11 which participate in non-classical pathways, potassium outflow through plasma membrane pores leads to activation of inflammasome NLRP3, and activation of classical pathways of caspase-1 which subsequently promotes the maturation of Pro-IL-1β and Pro-IL-18.

IL-1β and IL-18 are the main proinflammatory factors released after pyroptosis, as well as HMGB1 and other endogenous host molecules. The role of IL-1β is mainly involved in in inflammation, vasodilation and immune extracellular review and also plays an important role in adaptive immune response [28]. IL-18 can promote the production of interferon γ (IFN-γ) in TH1 cells, NK cells and cytotoxic T cells to promote the development of TH2 cells and participate in local inflammatory reactions [29]. ASC spots of pyroptosis are released into the extracellular environment to promote the activation of inflammasome which together act as triggers, amplifies, and perpetuates pyroptosis signals.

Pyroptosis and airway microflora

Respiratory infections are still one of the major causes of morbidity and mortality worldwide, and with the culture of anaerobic bacteria in the 1950s, the research on microbiome began [30]. For a long time, the normal immune lower respiratory tract has been considered as a sterile environment for growth. With the application of systems biology techniques, researchers have taken advantage of the characteristics of bacteria that all contain 16S rRNA genes. 16S rRNA gene sequencing has been widely used to identify the similarity of nucleotide sequences of bacteria species and genera. The advent of metagenomics has taken microbiome research one step further. There is growing evidence that the respiratory tract also has a unique microbiome which is not colonized until after birth. And there is a balance between the flora, once the balance is broken, it will threaten the respiratory homeostasis. In addition, airway microbes are not only composed of bacteria, but also fungi and viruses can interrupt the balance of the microbiome. However, there are few studies on the viral and fungal groups. With the progress of molecular

technology, future studies will definitely focus on the detection of airway fungi and viruses.

Lower respiratory tract microbiota composition and oral and nasal microbial composition is different. The lower respiratory tract microbiota to less than the density of the upper respiratory tract and microbes have significant diversity. Few studies have shown that healthy adults alveolar lavage fluid and lung microbiome mainly consists of four types of bacteria door, it main includ Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes. The main genera of lower respiratory tract include Prevotella, Pseudomonas, Veronella and Streptococcus [31]. The main factors affecting its composition are microbial migration, microbial clearance and relative reproductive rate of its members. The ingoing of microbes mainly with air suction, trace aspiration and upper respiratory tract associated microorganisms disseminated. Microbial removal depends on ciliary movement, cough and immunity, etc. The relative reproduction rate of microorganisms depends on the partial pressure of oxygen in the airway, pH, temperature, humidity, relative blood perfusion, anatomy, sedimentation of inhaled particles and immune cells. During lung disease, the balance of all three is disturbed, resulting in an imbalance of the species. When triggered by inflammation such as infection and exposure to allergens, the growth conditions of respiratory tract flora will be changed. The increase of mucus provides applications for bacterial growth. Oxygen partial pressure, pH value and temperature in the airway make bacteria selectively grow, and the killing effect of inflammatory cells will also select bacterial species and break the balance of airway flora. The new dominant strain then triggers a stronger respiratory immune response, and the cycle repeats. When the airway microbiome is unbalanced, it can be associated with asthma, chronic obstructive pulmonary disease, pulmonary cystic fibrosis, idiopathic pulmonary fibrosis and so on. For example, cigarette entering the airway will damage epithelial cells and promote microbial entry into the human body. In the lavage fluid samples of chronic COPD and healthy people, it was found that the diversity of microbiome decreased, including streptococcus, Prevotelli, Pseudomonas and Haemophilus. In the field of bronchial asthma, microbiome diversity is negatively correlated with the incidence of asthma [32]. The use of antibiotics in childhood increases the risk of asthma and allergic diseases. Proteobacteria predominate in the lower respiratory tract of asthmatics, and increases in

Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae can lead to childhood asthma. The proportion of Pseudomonas aeruginosa and Burkholderia increased in 23 patients with cystic fibrosis which is characterized by defective ciliary clearance of airway mucus and chronic infection with complex microbiota.

Bacterial infection is sensed by pattern recognition receptors and produces NF-κB-dependent inflammatory cytokines, including the TNF superfamily of inflammatory cytokines which promote further inflammatory signaling through death receptors (TNFR1, Fas, TRAIL-R, and DR3). Pattern recognition receptors and death receptors together signal through adaptor proteins (TRADD, FADD, RIPK1) and participate in downstream signaling pathways to promote cell death. Inflammatory caspase plays an important role in host defense against pathogens. The inflammatory body sensor detects bacterial PAMP and adaptor ASC. Caspase activation can be recruited to initiate pyroptosis. There has been much evidence for the correlation between pyroptosis and airway microbiota. As an active antioxidant defense enzyme, glutathione oxidase 4 (GPX4) is a negative regulator of macrophage pyroptosis. Reduced GPX4 levels in bone marrow cells lead to caspase-11 activation and GSDMD lysis. The N-terminal fragment of GSDMD triggers pyroptosis in a phospholipase dependent manner which leads to the aggravation of sepsis in the multi-microbial infected mouse model [33]. NLRC4 inflamomes rely on the NLR family of inhibitor of apoptosis proteins (NAIPs) to sense bacterial components in the cytoplasm and detect flagellin of bacteria or the inner rod or protein components of bacterial type III secretion system. When infected with pseudomonas aeruginosa, Salmonella typhi and Burkholderia thaii in mice, NLRC4 can be activated by interferon regulatory factor 8 to regulate pyroptosis [34]. NLRC4 inflammasome can recognize Gram-negative bacteria such as Pseudomonas aeruginosa, Salmonella typhi, Burkholderia Thailand, Legionella pneumophila, Brucella, etc. [34-36]. Exotoxins secreted by Gram-positive bacteria and some gram-negative bacteria can be recognized by NLRP1 and NLRP3 inflammasome through ion-carriers, pore-forming agents, proteases and other mechanisms and begin to rely on the classic caspase-1-mediated cell pyroptosis. In addition, the N-terminal fragment of GSDMD can directly kill bacteria outside the host, including Escherichia coli, Staphylococcus aureus, listeria, etc., these processes is

caused by the fact that its N-terminal domain can combine with cardiolipin on bacterial cell membrane and form pores after the polymerization [37]. LPS is a component of the cell wall surface of Gram-negative bacteria. Under LPS stimulation, caspase-11-mediated activation in a non-classical way can bind specifically to LPS lipid A, trigger caspase-11 oligomerization, lyse GSDMD and open cell membrane pores to induce cell pyroptosis. In addition, caspase-11 oligomization can also lyse the half-channel gap junction protein 1 (Pannexin-1), resulting in the release of intracellular ATP through the channel to the extracellular and activate the P2X7 receptor to open the channel and induce cytoskeleton and membrane destruction. Other studies have found that when the host is infected, many microorganisms are found in neutrophils involved in cell pyroptosis, such as Salmonella, Neisseria gonorrhoeae, Staphylococcus aureus, Chlamydia pneumoniae, Listeria, etc. [38].

Pyroptosis is an inflammatory pathway of programmed death. In addition to bacteria, fungi, DNA and RNA viruses can activate inflammasome to induce pyroptosis [39,40]. For example, Candida (37.91 %) was most common in the lower respiratory tract, followed by Aspergillus (16.99 %). Studies have found that caspase-11 can control the progression of aspergillus in vivo under interferon and other initiation signals during aspergillus infection and fungal hyphae development and or phagocytic neutralization are required in pyroptosis induced by Candida albicans [41,42]. However, the physiological effects of pyroptosis on fungi are still unclear. In human immunodeficiency virus (HIV) infection, HIV-1 recognition by DNA sensor IFI16 down-regulates viral replication in macrophages and accelerates pyroptosis of CD4+T cells [43]. Caspase-1 and caspase-11-mediated pyroptosis are important in mouse models against influenza a and West Nile virus infection [44,45]. During cytomegalovirus, vaccinia virus, human papillomavirus and Plasmodium infection, microorganisms can activate AIM2 inflammasomes by releasing DNA into the host cytoplasm [40]. In the field of respiratory diseases or anti-infection, treatment seems to have entered a dilemma. As the case of resistance to repeated antibiotic application after Pseudomonas aeruginosa infection, pyroptosis may provide a better idea.

Pyroptosis and airway epithelium

In lower respiratory tract infection, airway epithelium mainly plays three roles in maintaining airway homeostasis: physical barrier function, innate immune defense function and ciliary clearance function [46]. When the host is in contact with a large number of allergens, air pollutants and microorganisms, the airway epithelium can provide an efficient physical barrier to trap harmful substances in the mucus of the airway mucosa and remove them by innate immunity and cilium movement. At the same time, the epithelial cells release different chemokines and cytokines to cause airway inflammation. Ciliated cells, basal cells, goblet cells and rod cells are the main components of airway epithelial cells. Ciliated cells contain a large number of cilia. Under the influence of Notch signaling pathway, it can differentiate into goblet cells and repair airway epithelium after injury. Goblet cell contains vesicles, able to mucin secretion to the inner surface of the respiratory tract, capture harmful substances and cilia clearance in balance. Basal cells are able to live as stem-like progenitors, immobilize epithelial cells by hemidesmosomes, and reestablish pseudostratified columnar epithelium. The rod-shaped cells could secrete proteins secreting globulin family and differentiate into ciliated cells and goblet cells. With the progress of modern research techniques, human airway epithelial has not only confined to the microscopic view. Single-cell transcriptome study changed the understanding of airway landscape. In addition to the traditional four cells, there is less than 1 % of the cellular components, such as, ion cell neuroendocrine cells, hill cells of chemical induction, isolation, etc. [47]. A large number of previous studies have shown that intestinal epithelial cells rely on continuous renewal to maintain tissue homeostasis and excessive intestinal epithelial cell death can lead to chronic inflammation [48-50]. Pyroptosis regulates chronic inflammation of the intestine by regulating microbial infection, secretion of IL-1β and IL-18, and lysosomal damage. This process explains how intestinal epithelial homeostasis is affected by cell pyroptosis. Airway epitheliumis also involved in pyroptosis which is derived from the same embryo as intestinal epithelium. Exfoliated epithelial cells are found in most patients with asthma [51]. When stimulated by allergens, caspase-1 protein is hydrolyzed and activated and then the epithelial cells of pyroptosis are induced to secrete IL-1β, driving extravasation, cell proliferation and differentiation, angiogenesis, wound healing, etc., it will regulate airway contraction and diastolic responses, thus affecting airway structural changes. The 17Q21 locus associated with asthma has been found to contain genes encoding ZPBP2,

GSDMB, IKZF3, ORMDL3, GSDMA and so on [52]. GSDMB-1 overexpression can up-regulate the levels of TGF-β1, 5-LO, MMP9, EOtaxin-3, CCL28, CXCL6, CXCL17, HSP60 and HSP70 in airway epithelium. GSDMB and GSDMD belong to gasdermin protein family. GSDMD play a pore-forming role and induce pyroptosis which can be lysed by inflammatory caspase to release the N-terminal domain. Das *et al.* found that GSDMB can mediate scortosis of cilia cells and trigger the release of IL-33, IL-1β and other cytoplasmic contents [53]. In addition, airway epithelium can also produce a secretory globulin (SCGB) 3A2 which can deliver LPS to cytoplasm in the form of a carrier through the cell surface receptor sundecan-1 to promote nonclassical cell pyroptosis [54].

The physical barrier function of airway epithelium mainly depends on the control of airway mucus which has antibacterial activity, including defensin, lysozyme, immunoglobulin, etc. MUC5AC and MUC5B are produced by secondary airway epithelial cells, forming the first layer of surface defense. The balance of MUC5AC and MUC5B is important in maintaining mucus. NLRP3 inflammasome activation signaling pathway promotes the production of MUC5AC and MUC5B. NLPR3 inflammasome is an intracellular multi-protein platform and can activates caspase-1 pathway to promote airway inflammation. Studies have shown that S100A8, S100A9, S100A12, etc. can promote the increase of NLRP3-activated airway epithelial MUC5AC, ATP can also promote the activation of NF-κB and NLRP3 activation to induce the production of airway epithelial MUC5AC, and participate in airway homeoregulation [55]. In the pathogenesis of asthma, the activation of NLRP3 inflammasome can promote the production of TNF-α and IL-13 cytokines and participate in the pathogenesis of airway mucus hypersecretion [56]. In addition, adhesion between epithelial cells also maintains physical barriers. Tight junctions (TJ) provide epithelial cells with ion penetration and limit the entry of microorganisms and macromolecules. Adhesion junctions located below TJ maintain epithelial integrity and desmosomes provide mechanical stability of the epithelium through interfilament cytoskeletal contact. Below the airway epithelial cells, plasma cells secrete immunoglobulin IgA which is transported to the epithelial surface by receptors and prevents airborne harmful substances from adhering. Epithelial cells contain pattern recognition receptors which are expressed at the top of the epithelium and the outer side of the base [57]. They can quickly perceive threats and initiate host immunity, inflammatory response and remodeling while cell pyroptosis is involved. In an experiment using irradiation of mouse airway epithelium to increase the fungal burden of Aspergillus fumigatus, the expression levels of Zonula occludens 1 (ZO-1) and epithelial cadherin (E-cadherin) at the epithelial barrier were decreased and NLRP3 inflammasome activation was increased after irradiation. A large amount of blood exudates and inflammatory cells gather which also increases our understanding of radiation pneumonitis, skin injury, oral mucositis and other diseases [58].

Pyroptosis and airway immunity

As the first line of host defense, epithelial cells participate in innate mucosal immunity. There are multiple pattern recognition receptors on their surface to facilitate the innate immune system to monitor intracellular and extracellular infectious agents. Therefore, once the airway barrier is breached, pathogenic microorganisms and harmful macromolecules are first perceived by airway epithelial cells which release cytokines and chemokines through MyD88 signal transduction to activate NF-κB, mitogen-activated protein, interferon regulatory factor and other cytokines, these can affect airway inflammation and airway immunity [59]. Therefore, the regulation of airway immune homeostasis not only depends on the role of immune cells, but also airway epithelium has immune characteristics, such as detection and clearance of dead cells, inflammatory memory and circadian rhythm adjustment [47]. In innate immunity, epithelial cells can create a microenvironment, it releases antimicrobial peptides such as defensin and immunoglobulins such as sIgA and inhibit macrophages and dendritic cells through the combined mediation of TGF-β and epithelial cell αVβ6 integrin [60-62]. In adaptive immunity, epithelial cells can play a recruiting role and coordinate with T and B lymphocytes.

The vast majority of pyroptosis caused by Gram-negative bacteria have been found in mouse macrophages. Lipopolysaccharide induced by Gram-negative bacteria can promote the amplification of macrophages and monocytes and stimulate inflammasome [63]. At the same time, some exotoxins can promote the release of cytokines by T lymphocytes. Studies have shown that natural killer cells and cytotoxic

T lymphocytes are lysed by the derived granulation enzyme A, resulting in the formation of pores of GSDMB and promoting pyroptosis [64]. However, GSDME can induce pyroptosis in tumor tissues to release chemokines (MIP-1β, MIP-2, IP-10, etc.) to recruit immune T cells [65]. Knockout of the mouse inflammasome resulted in a general decrease in T cell response [66]. In some way, viral pyroptosis can aggravate ARDS. Overactivation of the inflammatory immune response leads to cytokine storm and subsequent immune failure [67]. Inflammatory factors released by pyroptosis can increase the level of TGF-β, stimulate the production of collagen and fibronectin in fibroblasts, promote the transformation of myofibroblasts, affect the contraction and relaxation of airway smooth muscle, and increase the levels of IgE, IL-1β and Th2-related cytokines. In addition, after pyroptosis of virus-phagocytosing macrophages, a large number of viral particles, cytokines, chemokines, etc. will be released which may lead to the deposition of immune complexes. Recent studies have shown that COVID-19 also activates NLRP3 inflammasomes by affecting cellular ion imbalance and damaging mitochondria to produce ROS [68].

TH17 cells participate in the host's immune defense and help maintain the mucosal barrier of airway epithelium. IL-1 deficiency can promote the reduction of TH17 production and T cell proliferation, indicating the key role of cell pyrosis in immune defense. The IL-1 cell family is immunogenic and controls the quality of CD4+T cell responses by influencing DC. IL-18 is another important medium of pyroptosis which can promote IFN-G production through memory CD8 in the absence of TCR receptor stimulation and other lymphocyte subsets can respond to IL-18 and IL-1. High migration family protein (HMGB1) is a key mediator of death from endotoxin. As a transporter, it has been found that it can bind nucleic acids, LPS, histones, IL-1α and nucleosome IL-1β to enhance the inflammatory response [69]. Molecules bound to HMGB1 can be entoxified through glycosylation end product receptors to activate immune sensors in the cytoplasm [70]. In addition, HMGB1 can act as DNA molecular chaperone and promote the activation of NF-κB, thus generating proinflammatory mediators and recruiting a large number of effector T cells, leading to the accumulation of CD8+T cells in the matrix [71,72]. In fact, the effect of pyroptosis on airway immunity is not only reflected in infectious diseases. In the immune microenvironment, CD8+T cells and NK cells can trigger tumor clearance through the GSDMB-granzyme A axis, and can also use the GSDME-granzyme B axis to induce pyroptosis [73]. Many immunostimulatory and antitumor effector genes was found to be associated with this.

Summary of pyroptosis in airway homeostasis

Recent research has significantly increased our understanding of pyroptosis, but the cells cascade signaling pathways of pyroptosis concrete mechanism is not entirely clear. Although the specific molecular mechanism is not clear, it can be concluded that pyroptosis does not exist independently and the molecular pathways are affected by apoptosis, necrosis and other death pathways. It is interesting to note that pyroptosis can provide a good idea in areas where drug-resistant bacterial infections cannot be overcome. Pyroptosis signals can also be activated by fungi and viruses, not just resistant bacteria. Pyroptosis as an inflammatory response, it can affects the homeostasis of the lower respiratory tract. In the regulation of airway homeostasis, chronic inflammation, immune response and pyroptosis interact with each other. Disruption of any of these processes, including airway microbiota changes, epithelial barrier destruction and immune impairment, it will lead to disruption of airway stability (Fig. 1). The ultimate goal of multicellular research is to prevent and solve human diseases. Therefore, most of our models are inspired by mice. However, the mucosal composition of mice and humans is not exactly the same. Cell pyroptosis is a key factor in airway homeostasis which is closely related to immunity, microbiota and epithelial barrier. In the study of airway diseases, the key points including inflammasome, Caspase, GSDMD, IL-1β, IL-18 and HGBM1 can provide ideas for the treatment of diseases.

Conflict of Interest
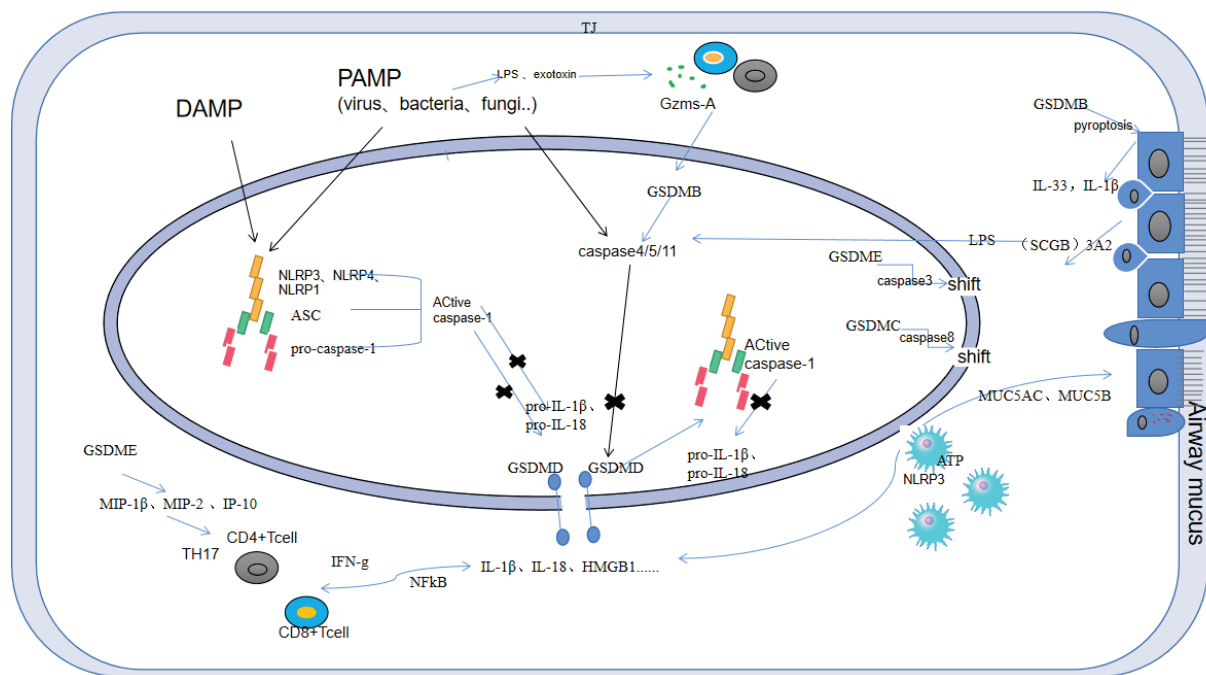There is no conflict of interest.

Acknowledgements

Fig. 1. The relationship between pyroptosis and airway microflora, airway epithelial structure and airway immunity. The outermost layer represents the airway mucosa, and the airway surface is mainly composed of four types of cells. They are involved in airway epithelial structure and affect pyroptosis. The cells in the figure show two types of pyroptosis pathways, one is the classical pathway dependent on caspase-1 dominance and the other is the non-classical pathway dependent on caspase-4, -5 and -11 dominance. When the airway senses a danger signal, innate immune cells recognize PAMP and DAMP through PRR which then assemble into a cascade of proteins called inflammasomes that activate caspase-dependent signaling pathways. Induced gasdermin pore formation, resulting in cell membrane rupture, release of IL-1β, IL-18, HMGB1 and so on. Airway microbe is the signal to activate pyroptosis, and airway immune cells are affected by inflammatory factors and react to pyroptosis. Airway microbe is regulated, and airway epithelium has immune function. Together they regulate and maintain airway homeostasis.

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