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Pyroptosis in Pediatric Mycoplasma pneumoniae Pneumonia: Mechanisms and Emerging Insights

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Abstract. Mycoplasma pneumoniae pneumonia (MPP) is one of the common infections of the pediatric respiratory tract, in which dysregulated immune responses drive much of the tissue inflammation. Pyroptosis mediated by inflammasome has become a leading way to promote inflammation. Activation of NLRP3 inflammasome activates cleaving of caspase-1 and the secretion of pro-inflammatory cytokines, aggravating local immune response. The role of pyroptosis in the initiation and aggravation of the pathology in MPP in children is already proved by studies. This review summarizes the existing advance of pyroptosis in pediatric MPP, aiming at providing the theoretical support to prevent and treat pediatric MPP.

Keywords: Pyroptosis, Mycoplasma pneumoniae, Pediatric pneumonia, Inflammasome

1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) is the main cause of community-acquired pneumonia (CAP) in children, especially school-age children and adolescents. Statistics show that infection with MP is responsible for approximately 10%~40% of CAP in children [1]. The pathogenesis of MPP is not only related to the injury mediated by pathogen directly, but it is closely related to immune dysregulation and excessive inflammatory responses [2]. Mycoplasma pneumoniae infection can mobilize human immunity through its membrane-associated lipoproteins, resulting in an increased level of pro-inflammatory cytokines that aggravate lung injury. Inflammation induced by immune system is considered a dominant part in MPP pathogenesis.

Recent discovery of pyroptosis as a type of programmed cell death has made a key contribution to studies of inflammation and infection. It is generally induced when the NLRP3 inflammasome is activated, which activates caspase-1, and activated caspase-1 initiates processing and release of proinflammatory cytokines such as IL-1β and IL-18, and processing of GSDMD to generate pores in the plasma membrane, leading eventually to lytic cell death [3, 4].

Pyroptosis has become an important mechanism that promotes inflammation and lung damage of MPP. Infection of Macoplasma pneumoniae stimulates the NLRP3-caspase-1 signaling pathway of immune cells to induce pyroptosis of immune cells and release of IL-1β, IL-18 and other pro-inflammatory factors to enhance local inflammatory responses and tissue damage [5, 6]. Elucidation of the role of pyroptosis in MPP provides new clues for understanding the pathogenesis of the disease and indicates new potential directions for treatment. In this respect, we summarize current

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studies on pyroptosis in children with MPP in this review, with the hope of providing a theoretical basis for better prevention and treatment strategies.

2. Core molecular pathways of pyroptosis

As an inflammatory programmed cell death, pyroptosis is induced by inflammasomes and gasdermin proteins. Pyroptosis is characterized by swelling of cells, formation of pores in plasma membranes and secretion of pro-inflammatory mediators, which are involved in infectious and inflammatory diseases. Both canonical and non-canonical pathways can induce pyroptosis. Regardless of the activation trigger, these two pathways eventually result in the activation of gasdermin proteins, thus facilitating inflammatory signaling cascades and induce tissue damage [7].

2.1. Canonical and non-canonical pyroptosis pathways

Pathogen- or damage-associated molecular patterns (PAMPs and DAMPs) are primary inducers of the canonical pyroptosis pathway. They are sensed by pattern recognition receptors (among which the inflammasomes have been most intensively studied). Upon stimulation, receptor oligomerisation induces recruitment of ASC and pro-caspase-1 to the inflammasome, in turn provoking auto-processing and activation of caspase-1 by caspase-1 [8]. Activated caspase-1 plays a dual role in the canonical pathway. Caspase-1 cleaves gasdermin D (GSDMD) into a release of its N terminus (GSDMD-NT). The GSDMD-NT inserts into the plasma membrane, after which GSDMD inserts into the cell forming oligomeric pores. At the same time, caspase-1 converts the pro forms of IL-1β and interleukin-18 (IL-18) into active IL-1β and IL-18, which exits from the cell through GSDMD pores, giving rise to and amplifying inflammatory signaling. In this way, the canonical pathway is the key that unlocks the pathogen sensor–inflammatory signaling–cell lysis.

Unlike the canonical pathway, non-canonical pyroptosis does not require a canonical inflammasome. Rather, the non-canonical pyroptosis is triggered when intracellular LPS is directly sensed by human caspase-4 or caspase-5 or mouse caspase-11. After being activated, caspase-4 or caspase-5 or caspase-11 cleaves GSDMD (gasdermin D), which forms a pore and consequently causes cell lysis [9]. The non-canonical pathway does not process IL-1β or IL-18 directly but can lead to the secondary NLRP3 inflammasome activation by release of ATP, by activation of pannexin-1 channels and potassium ions efflux, and further magnify the inflammatory process.

In addition, pyroptosis is subject to many levels of regulation. Inflammasome activation is dependent on different upstream signals, such as potassium efflux, lysosomal rupture, mitochondrial production of ROS, which all promote NLRP3 and other inflammasomes activation. The activity of GSDMD is also regulated beyond caspase-mediated cleavage, as posttranslational modifications can modulate membrane localization of GSDMD and pore formation. Although pyroptotic membrane rupture takes place, it can be reversed to a certain extent through ESCRT-III complex and the cell can restore membrane integrity and reduce cell death and tissue inflammation-induced damage [10].

2.2. Role of the gasdermin family in pyroptosis

Within the gasdermin family, GSDMD is the major gasdermin effector protein, being the major effector of pyroptosis. Under resting conditions, GSDMD is inactive through intramolecular inhibition of its N terminus and C terminus. After cleavage by caspases, the GSDMD N-terminal fragment is released and oligomerizes. The N-terminal fragment then inserts into the plasma membrane's inner leaflet and assembles into pores by binding to phosphoinositides and cardiolipin,

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with a pore size of about 10–20nm. These pores trigger a loss in membrane integrity, increased permeability, cell swelling and membrane rupture.

GSDMD pores have pore channels for release of inflammatory mediators. Through pores, mature inflammatory cytokines, such as IL-1β (interleukin-1β) and IL-18 (interleukin-18), are quickly released and then activate adjacent immune cells, elevate the inflammatory response and so on. After membrane rupture, a large amount of DAMPs are released into the extracellular space. These DAMPs will further activate the immune activation and construct a self-amplifying inflammation loop to cause or aggravate pathological change in infectious diseases [11].

However, besides GSDMD, pyroptosis process also involves other gasdermin proteins. Caspase-3 is an apoptosis-related caspase. Caspase-3 cleaves gasdermin E (GSDME) and can release its N-terminal fragment to generate membrane pores, which leads to the conversion of apoptosis to pyroptosis, aggravate tissue damage and facilitate the development of inflammation [12]. Furthermore, the expression of gasdermin in various cell types has differences, so their functions might be different for various tissues or in diseases.

3. Role of pyroptosis in the pathogenesis of pediatric MPP

Mycoplasma pneumoniae (MP) infection stimulates inflammasome signal pathways and gasdermin-related signal pathways by multiple mechanisms, inducing the release of pro-inflammatory cytokines, finally causing tissue damage and aggravating the course of disease and chronic progression.

3.1. Molecular mechanisms of MP-induced pyroptosis

MP as a cell wall–deficient prokaryotic organism, its pathogenicity depends largely on membrane lipoproteins and virulence factors of MP. After infection, pathogen-associated molecular pattern is recognized by the host innate immune system. MP lipoprotein binds with Toll-like receptors, especially TLR2 and TLR4, inducing NF-κB signaling, which promotes the expression of various genes related to inflammasome [12]. At the same time, cytoplasmic MP DNA is recognized by AIM2 inflammasome, directly contributing to inflammasome activation [13].

Among the MP virulence factors, CARDS (community-acquired respiratory distress syndrome) toxin is the most important virulence factor in pathogenesis of MP. It is reported that CARDS toxin could induce ROS production and induce potassium efflux, which are both important factors for the activation of NLRP3 inflammasome [14]. In addition to the facilitation of conformation activation of NLRP3 by ROS, ROS also cause mitochondrial injury to facilitate mitochondrial DNA liberation and enhance inflammatory signals.

Mycoplasma pneumoniae activates the NLRP3 inflammasome in alveolar macrophages and airway epithelium, which increases caspase-1 activity. Caspase-1 cleaves GSDMD to form pores in the plasma membrane and promotes maturation and secretion of IL-1β and IL-18 and canonical pyroptotic cell death of the host cell in response to Mycoplasma infection [15]. At the same time, the AIM2 inflammasome recognizes cytosolic MP DNA and might also participate in this process; thus, multiple inflammasome pathways cooperate to drive pyroptosis in the MP infection.

3.2. Pyroptosis-mediated pulmonary inflammation and tissue injury

Although the pathophysiological importance of pyroptosis in MPP is mostly reflected in the amplification of inflammatory reaction, alveolar macrophages and airway epithelial cells undergoing

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pyroptosis also rapidly release large amounts of IL-1β and IL-18, two types of molecules that promote inflammation. IL-1β recruits neutrophils, causes fever and induces the synthesis of acute-phase proteins, and IL-18 boosts the immune system, inducing interferon-γ (IFN-γ) expression and enhancing the activity of T helper 1 (Th1) cells as well as NK cells.

In cases of Mycoplasma pneumoniae infection, excessive production of these cytokines causes an overly activated local inflammatory response and may even result in an immune equilibrium similar to a "cytokine storm". Clinical research shows that children with severe MPP often have high levels of IL-1β, IL-18 and other proinflammatory molecular signals, which are closely related to symptoms such as high fever, respiratory distress, and more serious pulmonary consolidation on the imaging finding of lung in the clinic [16]. These results indicate that pyroptosis is the key factor of inflammatory aggravation in MPP. In addition to cytokine production, pyroptosis also directly causes structural damage to the lungs. Proper integrity of the respiratory barrier depends mainly on airway epithelial cells. The pyroptotic death of airway epithelial cells leads to rupture and shedding of membranes and damage to the epithelial barrier, increased vascular permeability, plasma leakage, and inflammatory cell infiltration. These pathological changes cause pulmonary consolidation and pleural effusion. In addition, DAMPs released from pyroptotic cells can further stimulate adjacent immune and endothelial cells, sustaining a cascade of inflammation.

At the clinical level, more evidence is accumulating to indicate the correlation between the level of pyroptosis-related markers and disease severity. Currently, some research shows that patients with severe MPP have dramatically higher expression of IL-1β and IL-18 in BALF and serum than patients with mild symptoms. Increased level of cell injury markers, such as lactate dehydrogenase (LDH), can also be found, which are positively associated with radiological severity scores [16]. These results indicated that pyroptosis-associated molecules not only involved in disease onset and development, but they can be potential indicators for evaluating disease severity.

3.3. Pyroptosis in immune evasion and chronic progression of MPP

Pyroptosis also plays a dual role in host defense. On the one hand, a desirable degree of pyroptosis helps to clear infected cells and causes secretion of inflammatory mediators, which increases adaptive immune responses. On the other hand, too much pyroptosis or prolonged pyroptosis during MP infection could cause immunopathology damage, which may result in persistent infection and immune evasion by the pathogen. Studies have shown that pro-inflammatory cytokines promote activation of vascular endothelium and immune cells, leading to systemic inflammatory response and multi-organ lesions [17]. Moreover, prolonged pyroptotic responses could also be linked to post-infectious manifestations of MPP, such as chronic cough and airway hyperresponsiveness. Persistent inflammation can cause repeated epithelial damage and poor wound repair mechanisms, resulting in fibroblast proliferation and extracellular matrix deposition, eventually leading to airway remodeling.

4. Therapeutic strategies targeting pyroptosis in pediatric MPP

With the latest understanding of the role of pyroptosis in MPP pathogenesis, targeting the signaling pathways of pyroptosis have become an important research idea. Focusing on important steps such as inflammasome activation, the gasdermin effector effect, effect on downstream cytokines release, the pursuit of innovative treatment options may provide new strategies for the management of severe MPP.

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4.1. Potential therapeutic targets within the pyroptosis pathway

4.1.1. Inhibiting inflammasome assembly and activation

The NLRP3 inflammasome is a key upstream controller of pyroptosis. Abnormal activation of NLRP3 results in a potent release of IL-1β and IL-18 and initiates the inflammatory chain reaction. Therefore, the NLRP3 is now a main target of present studies. MCC950 is the best representative small-molecule NLRP3 inhibitor. It could specifically inhibit NLRP3 inflammasome, therefore inhibiting the binding of caspase-1 and inhibiting GSDMD cleavage and secretion of cytokine. Animal experiments have proved that MCC950 remarkably reduces inflammation and tissue damage, and shows promising therapeutic value for the infection-induced inflammatory diseases [18]. Besides MCC950, new inhibitors like CY-09 inhibit inflammasome activation by blocking ATP binding sites and have strong anti-inflammatory efficacy in different models [19].

Moreover, intervening in upstream signaling cascades has great potential. As ROS strongly trigger the activation of NLRP3, antioxidants such as N-acetylcysteine (NAC) can indirectly inhibit this step by scavengenging ROS, decreasing pyroptosis levels [20]. This kind of 'upstream' regulation is wide applicational.

4.1.2. Blocking GSDMD pore formation

As the main effector of pyroptosis, GSDMD-mediated generation of membrane pores are a crucial step for both cell lysis and inflammatory cytokine release. Therefore, directly inhibiting GSDMD activity is another effective therapeutic strategy. Several recent studies report that disulfiram, a known clinical drug, can covalently modify key cysteine residues of GSDMD. Such modification blocks the oligomerization and pore formation of GSDMD, remarkably inhibiting the pyroptotic process [21]. This drug repurposing strategy offers a quick track approach to get the targeted treatment to practice, which is particularly beneficial during an acute inflammatory response. Given their established safety profiles, these existing medications are expected to accelerate the transition from basic research to clinical application.

4.1.3. Neutralizing inflammatory cytokines

Because the massive release of inflammatory factors is the consequence of pyroptosis, targeting of downstream cytokines is very simple intervention. Currently, cytokines downstream of IL-1β are being targeted in various inflammatory diseases, and therapeutic intervention in these drugs has achieved satisfactory clinical benefits. Anakinra and canakinumab can interrupt the signal transduction of IL-1 signal and further relieve inflammation [22]. In cardiovascular and autoinflammatory diseases, blocking IL-1β has been quite successful in lowering inflammation and prognosis, thereby providing theoretical basis for using IL-1β-targeting drugs in severe MPP. However, as current research results are largely indirect evidence, the validity and safety of this approach to pediatric MPP still need further validation in rigor clinical trials.

4.2. Current challenges and future directions

4.2.1. Limitations of cellular and animal models

Most of the existing studies about pyroptosis during MPP rely largely on in vitro cell culture or mouse experimental models. Mycoplasma pneumoniae is mostly strictly host-specific, and humans

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are the natural host for MP. Infection responses between mice and humans differ, so conventional animal models cannot sufficiently simulate the true underlying pathology of pediatric MPP. Such limitations naturally make it difficult to translate bench discoveries to the bedside application. To increase the extrapolation of the experimental results, efforts towards the future studies need to improve and more precisely simulate the physiology characteristics of humans, like humanized mice or organoids.

4.2.2. The therapeutic window and immune balance

During the early phases of infection, pyroptosis is important for protection, as it kills infected cells and stimulates immune inflammation signals to enhance the immune defense function. On the other hand, hyperactive pyroptosis results in runaway inflammation and collateral organ damage. The central challenge of pyroptosis-targeted therapeutic intervention is to restrain the detrimental inflammation while preserving essential anti-infective immunity. To pinpoint the critical therapeutic window is particularly important. Over-blocking during the early phase of the disease would compromise pathogen elimination; over-suppression in the hyperinflammation phase can bring significant benefit to patients. Therefore, future studies should emphasize adaptive regulation strategies. Appraisal of effectiveness and safety of combination therapies, for example, combination use of antibiotic with pyroptosis inhibitor, will be crucial to realize a tightly-balanced immune system defense and inflammation regulation.

4.2.3. Development of biomarkers

At present, the lack of specific clinical indicators that can accurately reflect in vivo pyroptotic activity naturally limits the implementation of precision medicine. Biomolecules such as GSDMD-NT, cleaved caspase-1, IL-1β and IL-18 detectable in plasma or bronchoalveolar lavage fluid have been suggested to be candidate biomarkers to evaluate pyroptosis [23]. Biological candidates hold promise for early prediction of children with high risk of severe MPP for stratified management and dynamic treatment of MPP. However, the diagnostic sensitivity and specificity of their biomarkers need validation in large clinical studies.

4.2.4. Personalized and precision medicine

Inflammatory responses to MP infection differ considerably in individuals, and thus the magnitudes of pyroptosis have a significant role for genetic factors. Genetic polymorphisms in loci such as NLRP3 and GSDMD can determine magnitudes of inflammasome activation and subsequent cytokine production, governing the progression and severity of the disease, as well as overall prognosis. Going forward, integrating multi-omics datasets to identify inter-individual differences in pyroptosis-related genes will provide a theoretical bedrock for individual MPP interventions. Meanwhile, developing targeted strategies for different inflammatory phenotypes (inspired by precision medicine) will undoubtedly become one of the driving directions for future advancements.

5. Conclusion

Pyroptosis is the key inflammatory event that propels the pathogenesis and development of pediatric MPP. After infection of MP, the activation of inflammasomes and the GSDMD pathway result in the burst export of cytokines. This cascade strongly boosts systemic inflammation and aggravates tissue injury in the lung. Although interventions that inhibit the pyroptotic pathway provide new options

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for the treatment of MPP, as a double-edged sword of pyroptosis protecting hosts from infection, the timely spatiotemporal regulation of pyroptosis is urgently needed. More extensive mechanism studies and translational research are in order. By finding appropriate biomarkers and tailoring regimens, the clinical treatment and outcome of severe pediatric MPP can be improved greatly.

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