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Research Progress on the Mechanism of GSDMD-Induced Pyroptosis in Macrophages

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Abstract: Pyroptosis is a form of programmed cell death. Excessive or uncontrolled pyroptosis and the production of pro-inflammatory cytokines can lead to organ damage, circulatory failure, and even death. Gasdermin D (GSDMD) is the primary executor of pyroptosis in macrophages. Upon cleavage, the N-terminal domain of GSDMD (GSDMD-N) is activated and oligomerizes to form pore-like structures in the plasma membrane, triggering pyroptosis and resulting in the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β). As a key executioner molecule of pyroptosis, Gasdermin D plays a crucial role in pathogen-induced pyroptosis in macrophages. With in-depth research on the function and regulatory mechanisms of GSDMD, its role in pathogen-induced macrophage pyroptosis has gradually been revealed. This article elaborates on the mechanism of GSDMD in pathogen-induced macrophage pyroptosis, providing insights for exploring pyroptosis in the prevention and control of bacterial diseases, and identifying new therapeutic targets for bacterial infections.

Keywords: GSDMD; Pyroptosis; Macrophages

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1. Introduction

Pyroptosis is a form of programmed cell death triggered by inflammasome activation, closely associated with host innate immunity and tumor immunotherapy [1]. Gasdermin D (GSDMD) is the key executioner molecule of pyroptosis. Upon inflammasome activation, GSDMD is cleaved into its N-terminal fragment (GSDMD-N), which possesses membrane pore-forming activity. This fragment oligomerizes to form pores in the cell membrane, leading to the release of cellular contents and inflammatory factors. During pathogen infection, macrophages, as a critical component of the immune system, recognize pathogen-associated molecular patterns (PAMPs) to activate inflammasomes, thereby inducing pyroptosis. Recent studies have confirmed the propagation of pyroptosis between cells. Pyroptotic cells secrete extracellular vesicles (EVs) carrying GSDMD pores, which are transferred

to bystander cells, resulting in pyroptosis of these bystander cells [2].

2. Pyroptosis

Pyroptosis is characterized by cell swelling, plasma membrane rupture, and the release of pro-inflammatory cytokines, damage-associated molecular patterns (DAMPs), and PAMPs [3]. As a crucial innate immune response, pyroptosis plays a significant role in defending against infections and endogenous danger signals. Its molecular mechanisms include the canonical pathway, non-canonical pathway, Caspase-3/8-mediated pathway, and granzyme-mediated pathway [4]. Pyroptosis eliminates damaged cells, thereby removing protective niches for pathogens, while simultaneously triggering inflammatory responses to combat intracellular infections. It is widely involved in the pathogenesis of infectious diseases, neurological disorders, and atherosclerosis. However, excessive pyroptosis can amplify inflammatory responses and cause harm to the organism. During pathogen infection, macrophages, as a critical component of the immune system, recognize PAMPs to activate inflammasomes, thereby inducing pyroptosis. GSDMD plays a central role in this process, as its activation and pore formation in the membrane are key steps in the occurrence of pyroptosis.

3. Macrophage pyroptosis

Cell death is a critical process in modulating host-pathogen interactions. Pathogen-triggered macrophage death manifests in various forms, including apoptosis, pyroptosis, necroptosis, and autophagic cell death [5]. Macrophage pyroptosis is an inflammatory form of cell death driven by the GSDMD protein family. During pyroptosis, inflammasomes are activated, leading to the cleavage of GSDMD and the release of its GSDMD-NT. These fragments form pores in the cell membrane, resulting in membrane rupture, cell death, and the release of large amounts of inflammatory cytokines and DAMPs, triggering a robust inflammatory response.

Studies have shown a close relationship between bacterial infections and pyroptosis. For example, *Streptococcus pneumoniae* can induce macrophage pyroptosis, while its expression of IL-6 can inhibit pyroptosis and alleviate associated inflammatory damage [6]; Macrophage pyroptosis can also mitigate infections by clearing *Mycobacterium tuberculosis* [7]; *Salmonella* infection induces inflammasome activation and macrophage pyroptosis, leading to inflammation and lethality [8]. It has been reported that secretions from pyroptotic macrophages upregulate gene signatures related to migration, cell proliferation, and wound healing, promoting wound closure and tissue repair in vivo [9]. The transcriptional regulation of GSDME (Gasdermin E) in macrophages and the role of GSDME-mediated pyroptosis in atherosclerosis provide new potential therapeutic targets for this condition [10].

With advancing research on pyroptosis, the molecular characteristics and regulatory mechanisms of the GSDMD family are gradually being elucidated, offering increasing insights into the treatment of host diseases and anti-pathogen infections.

4. The role of GSDMD in pathogen-induced pyroptosis

4.1. Overview of GSDMD protein

GSDMD is a mediator of inflammatory cell death triggered by the sensing of invasive infections and danger signals in the cytoplasm. Upon activation, GSDMD forms pores in the cell membrane, releasing pro-inflammatory

cytokines and disrupting membrane integrity, thereby inducing inflammatory cell death. The human GSDM family comprises six members: GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and DFNB59. Among these, GSDMD is the key effector molecule of pyroptosis.

GSDMD is encoded by the GSDMD gene located on chromosome 8q24.3 and serves as the primary executor of inflammasome-driven pyroptosis [11]. The GSDMD protein features two characteristic domains: the pore-forming GSDMD-N domain and the inhibitory C-terminal domain (GSDMD-C). In resting cells, GSDMD-N interacts intramolecularly with GSDMD-C, resulting in autoinhibition of full-length GSDMD. Cleavage of GSDMD is typically mediated by inflammasome-activated Caspase-1 or LPS-stimulated Caspase-4/5/11, leading to the release of GSDMD-N [12]. In addition to activating GSDMD, Caspase-1, a canonical member of the Caspase family, also cleaves pro-IL-1β and pro-IL-18 into their active forms, promoting their maturation and secretion. In highly activated cells that do not undergo pyroptosis, the inner diameter of GSDMD transmembrane pores determines the release of intracellular proteins, facilitating the secretion of inflammatory cytokines such as IL-1β and IL-18, while filtering larger proteins like high-mobility group box 1 (HMGB1, 150 kDa) and lactate dehydrogenase (LDH, 140 kDa) [13]. Therefore, the release of LDH is considered a hallmark event of pyroptosis.

4.2. GSDMD and bacterial infection

Bacterial infections can induce pyroptosis, and GSDMD plays a critical role in controlling microbial infections by regulating cytokine release and cell death. Studies have found that when intracellular infections are triggered by pathogens such as bacteria or viruses, the inflammasome signaling pathway is activated, ultimately leading to the cleavage and activation of the pore-forming protein GSDMD, releasing its N-terminal domain with pore-forming activity. The GSDMD-N oligomerizes to form pores in the cell membrane, causing cell rupture, pyroptosis, and the release of cytoplasmic contents, thereby inducing a strong inflammatory response to eliminate pathogens or clear endogenous harmful factors [1].

Subsequently, the involvement of other GSDM family proteins (GSDMA-E) in mediating pyroptosis has been discovered. Since the activation of GSDM proteins is not solely dependent on inflammatory caspases, pyroptosis has been redefined as a regulated cell death mediated by GSDM proteins [14, 15]. Research indicates that GSDMD is central to controlling infections caused by *Rotavirus* and *Salmonella*, GSDMD is also essential for inhibiting infections by *Brucella* [16], *Legionella pneumophila* [17], *Burkholderia thailandensis* [18] and *Francisella* [19].

Additionally, the direct antibacterial effect of GSDMD on bacterial membranes expands the mechanisms for restricting microbial growth and dissemination. However, the activation of GSDMD is a double-edged sword. For instance, the absence of Caspase-11 or GSDMD protects mice from septic shock in sepsis models [20]. Excessive activation of pyroptosis can lead to increased release of DAMPs or danger signals.

4.3. GSDMD and pyroptosis

GSDMD is a key effector of pyroptosis. In the context of bacterial infections, GSDMD-mediated pyroptosis can be driven by various molecular signaling pathways. Bacteria can activate both canonical (NLRs) and non-canonical (Caspase-11/4/5) inflammasomes through multiple mechanisms, processing GSDMD into its bioactive N-terminal fragment. The GSDMD-N fragment oligomerizes and forms pores in the host cell membrane, leading to pyroptosis [21].

Most studies suggest that pyroptosis is beneficial for host defense. For instance, during intracellular bacterial infections, the formation of GSDMD pores and subsequent cell lysis effectively disrupt the niche of invading

pathogens, reducing pathogen replication and evasion of the immune system. Additionally, the formation of GSDMD pores downstream of inflammasome signaling during pyroptosis releases cellular contents, including processed pro-inflammatory cytokines, LDH, nuclear DNA, and mitochondrial components. These molecules can act as DAMPs for the immune system, effectively enhancing inflammation and recruiting various immune cells to induce a localized antibacterial response [22].

4.4. GSDMD and disease pathogenesis

GSDMD-induced pyroptosis plays a crucial role in defending against pathogen infections and DAMPs by promoting the clearance of infected or damaged cells. However, sustained GSDMD-mediated pyroptosis can lead to ion flux dysregulation, organelle dysfunction, and excessive inflammatory responses, contributing to the onset and progression of various inflammatory diseases. These include, but are not limited to, diabetes, liver diseases, cardiovascular diseases, neurodegenerative disorders, intestinal diseases, and bloodstream infections. Pathophysiologically, GSDMD-mediated pyroptosis exacerbates the development of different inflammatory diseases [23]. Clinical studies have identified GSDMD as a potential diagnostic and prognostic marker for various diseases. Additionally, certain preclinical studies have discovered potential GSDMD inhibitors and other therapeutic agents to counteract GSDMD-mediated suppuration and inflammation.

5. Summary and perspectives

With in-depth research on the functions and regulatory mechanisms of GSDMD, its role in inflammatory responses has gradually been revealed. GSDMD-mediated pyroptosis has been shown to protect the host against bacterial infections. However, excessive GSDMD-mediated pyroptosis can lead to organelle dysfunction, cytokine storms, and harmful inflammation, contributing to the development and progression of various diseases. Inhibition or knockout of GSDMD has demonstrated protective effects in animal models of multiple inflammatory diseases, such as sepsis and other inflammatory disorders. Although significant progress has been made in understanding GSDMD-mediated pyroptosis, the specific mechanisms of GSDMD in different pathogen infections require further investigation.

Additionally, the specific roles of other members of the GSDM family in pyroptosis, pathogen evasion strategies targeting GSDM proteins, and how to leverage these findings to develop novel therapeutic strategies remain areas for further research. In summary, research on GSDMD highlights its critical role in bacterial infection-induced pyroptosis, with significant physiological and pathological implications. GSDMD may serve as an important therapeutic target for related diseases. The mechanisms of host inflammatory responses and tissue damage, as well as the intercellular transmission mechanisms of GSDMD and its role in diseases, provide new insights for future treatments.

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Disclosure statement

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