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Research Progress of PANoptosis in Central Nervous System Related Diseases

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Abstract: *PANoptosis is a form of inflammatory programmed cell death that is regulated by the PANoptosome complex and has key features of pyroptosis, apoptosis, and necroptosis, but cannot be fully characterized by any single pathway of programmed cell death. As an emerging form of cell death, PANoptosis plays a crucial role in the pathological processes of central nervous system diseases such as cerebral ischemia-reperfusion injury, sepsis-associated encephalopathy, Alzheimer's disease, and glioma. This article reviews the discovery, regulation mechanism and research progress of PANoptosis in different central nervous system diseases, aiming to provide reference and theoretical basis for basic research and clinical treatment of central nervous system diseases.*

Keywords: *PANoptosis, PANoptosome, programmed cell death, nervous system disease*

1. Introduction

PANoptosis is a novel inflammatory programmed cell death regulated by the PANoptosome complex with key features of pyroptosis, apoptosis, and necroptosis. Inhibition of a single programmed cell death pathway cannot suppress PANoptosis, while targeting the PANoptosome can prevent this type of cell death. The concept of PANoptosis was initially proposed in the study of infectious diseases, and as research progresses, its role in neurological diseases has attracted increasing attention. We have summarized the concept of PANoptosis, its regulatory mechanisms, and research reports on its involvement in neurological diseases, in order to deepen the understanding of PANoptosis in CNS diseases and provide new insights for clinical diagnosis, treatment, and therapy.

2. The definition of PANoptosis

PANoptosis is a new mode of procedural death proposed by American scholar Malireddi and others in 2019[1]. PANoptosis is regulated by the PANoptosome complex and has key features of Pyroptosis, Apoptosis, and/or Necroptosis.

Apoptosis refers to the process of a cell ending its life autonomously under the control of genes, which plays an important role in maintaining the number of normal cells in the organism, the development of tissues and organs, and the elimination of senescent pathological cells, and is the earliest PCD found[2]. Apoptosis is mediated by enzymatic reactions of the Caspase family and is usually initiated by both exogenous pathways (through death receptors such as Fas and TNF receptors) and endogenous pathways (through regulation by mitochondria and the Bcl-2 protein family). Morphological features include cell shrinkage, concentration of nuclear chromatin, formation of apoptotic bodies, and intact cell membranes[3]. Necroptosis differs from Necrosis in that it is regulated by membrane receptors and intracellular transduction molecules, and targeted inhibition of key molecules can inhibit the necrosis. Different from apoptosis, it forms holes in the cell membrane, causing multiple DAMPs to leak out, damage adjacent cells, and aggravate inflammation[4]. Pyrodeath is mainly mediated by inflammasome (e.g. NLRP3) and Gasdermin protein family. By activating Caspase-1, the inflammasome cleaved Gasdermin-D protein, released its n-terminal part, and embedded into the cell membrane to form pores, resulting in cell membrane rupture. This process is accompanied by the release of pro-inflammatory cytokines such as IL-1β and IL-18. The morphological features of pyroptosis include cell swelling, cell membrane rupture, and release of cell contents outside the cell[5]. These three programmed cell death modes are also the source of the "P," "A," and "N" in PANoptosis terminology, but PANoptosis cannot

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be explained by any of these three programmed death pathways alone.

In previous studies, apoptosis, pyrodeath and necrotic apoptosis were generally thought to operate independently, but with the deepening of research, more and more research results show that there is some crosstalk among the three, and they can cross-regulate each other[6]. For example, Caspase-8 is the initial caspase of exogenous cell apoptosis and inhibits the necrotic apoptosis mediated by RIPK3 and MLKL[7]. Caspase-3 and Caspase-7 can inactivate GSDMD through amino terminal division, and can also lyse GSDME, which changes the cell death form from apoptosis to pyrodeath. bcl-2 not only inhibits apoptosis by neutralizing proteins containing the BH3 domain, but also reduces cell pyrodeath by interacting with the BH3-like domain of GSDMD, and at the same time restricts the phosphorylation and oligomerization of MLKL to slow down necrotic apoptosis, thereby synthesizing and regulating multiple cell death pathways and maintaining the balance between cell survival and death[8]. These findings revealed complex interactions between cell death pathways and led to the concept of PANoptosis.

The discovery of PANoptosis has revealed the complex interplay and regulatory network among cell death pathways, providing a new perspective for understanding the role of cell death in diseases.

3. The regulation of PANoptosis

PANoptosis is regulated by a cascade of upstream receptors and molecular signals assembled into a polymer complex called PANoptosome[9]. PANoptosome is a multiprotein complex that provides a molecular scaffold that allows for the coupling and binding of proteins or molecules required for pyrodeath, apoptosis, and necrotic apoptosis[10]. These complexes can respond to a variety of stimuli, including viral infections, and involve a variety of sensors and regulators to initiate cell death. Five kinds of upstream PANoptotic molecules have been identified, namely ZBP1, AIM2, RIPK1, NLRP12 and NLRC5, which can sense specific stimuli and trigger the assembly of PANoptotic bodies to form PANoptotic bodies with different sensors and regulatory factors. Namely, ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, NLRP12-PANoptosome, and NLRC5-PANoptosome.

3.1 ZBP1-PANoptosome

Z-dna-binding protein 1 is an innate immune receptor protein that recognizes viral RNA products as well as endogenous nucleic acid ligands, such as Z-RNA[11]. During influenza A virus infection, ZBP1 interacts with RIPK3 and caspase-8 through its Zα domain to form a cell death signaling complex that activates the NLRP3 inflammasome, leading to pyrodeath, apoptosis and necrotic apoptosis[12]. Loss of the ZBP1 and Zα2 domains leads to reduced NLRP3 activation (pyroptosis), decreased cleavage of CASP-3, CASP-8, and CASP-7 (apoptosis), and decreased MLKL phosphorylation (necrotic apoptosis), suggesting that ZBP1 and its Zα2 domain play a key role upstream of PANoptosis.

3.2 AIM2-PANoptosome

AIM2 is a cytoplasmic double-stranded DNA sensor capable of recognizing double-stranded DNA (dsDNA) in the cytoplasm[13]. When a pathogen invades or a cell is damaged, dsDNA is released into the cytoplasm, and AIM2 binds to dsDNA via its HIN-200 domain, thereby activating downstream signaling pathways. In herpes simplex virus type 1 (HSV1) infection, AIM2 acts as a sensor to recognize dsDNA released by the virus, trigger the formation of AIM2-panoptosome, induce PANoptosis in host cells, and play an antiviral defense role[14]. Mice lacking AIM2 were more sensitive to HSV1 infection and had increased mortality, illustrating the importance of AIM2-panoptosome in antiviral infection.

3.3 RIPK1-PANoptosome

Receptor-interacting protein kinase 1 (RIPK1) is an upstream regulator in the TNF signaling pathway and is considered a key signaling node for regulating gene activation and the induction of cell death[15]. Under certain stimulatory conditions, such as Yersinia infection or transforming growth factor β-activated kinase 1 (TAK1) inhibition, RIPK1 assembles with other molecules like NLRP3, ASC, caspase-8, and FADD to form the RIPK1-PANoptosome complex. The formation of the RIPK1-PANoptosome further activates multiple cell death execution molecules, including caspase-3, caspase-7, GSDMD, GSDME, and pMLKL[16]. These execution molecules have the function of forming membrane pores, leading to cell membrane damage and ultimately causing the lytic death of cells, which is known as PANoptosis.

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3.4 NLRP12-PANoptosome

NLRP12 is a member of the NOD-like receptor (NLR) family and is a cytoplasmic innate immune sensor that can sense pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), playing an important role in inflammatory responses and cell death[17]. Upon stimulation by heme, pathogen-associated molecular patterns (PAMPs), or tumor necrosis factor (TNF), NLRP12 assembles with other molecules such as NLRP3, ASC, RIPK3, and caspase-8 to form the NLRP12-PANoptosome complex, mediating cell death through a caspase-8/RIPK3-dependent pathway[18].

3.5 NLRC5-PANoptosome

NLRC5 is another member of the nucleotide-binding domain leucine-rich repeat-containing (NLR) family and is associated with inflammation and infectious diseases, but its function as an innate immune sensor and cell death regulator is not well understood[19]. Research has found that under the stimulation of specific ligands, such as PAMP/DAMP (e.g., heme) and DAMP/cytokine combinations, NLRC5 interacts with NLRP12 to form the NLRC5-PANoptosome complex, triggering inflammatory cell death. The expression and activity of NLRC5 are regulated by TLR signaling and NAD+ levels, which together influence cell death[20].

These PANoptosomes are composed of different sensors, adaptors, and catalytic effectors. When encountering triggering factors such as different microbial infections and changes in cellular homeostasis, they can interact with each other and recruit other molecules to form the PANoptosome, thereby inducing the activation of caspase-3/7, the cleavage of GSDMD and GSDME, and the phosphorylation of MLKL, leading to pore formation in the membrane and the progression of PANoptosis[21].

The activation of PANoptosis and the formation of PANoptosome complexes enable the body to effectively resist the invasion of foreign pathogens. As the interactions between various pathways of programmed cell death become increasingly clear, it has gradually been recognized that targeting the regulation of a single cell death pathway, without considering the other pathways that occur simultaneously, may not yield the desired therapeutic effects. Therefore, interfering with or blocking key sensors on the PANoptosis pathway or inhibiting the formation of PANoptosome complexes can help find more effective treatment methods. PANoptosis can be considered the most complex form of cell death known to date. It encompasses the characteristics of pyroptosis, apoptosis, and necroptosis, yet it cannot be characterized by any single form of death, making it highly valuable and promising for research.

4. PANoptosis and neurological diseases

4.1 PANoptosis and ischemia-reperfusion injury

Cerebral ischemia is one of the leading causes of disability and death worldwide. The primary cause is the obstruction of blood flow to the brain due to arterial blockage, leading to a lack of nutrients and oxygen in brain tissue, which triggers the death of a large number of neurons[22]. Previous studies have observed PANoptosis in ischemic stroke rat and mouse models. Research has shown that mesenchymal stem cell transplantation reduces brain inflammation by suppressing splenic inflammation, thereby decreasing the expression of PANoptosis-related proteins and alleviating PANoptosis damage. Moreover, repetitive transcranial magnetic stimulation, under the condition of mesenchymal stem cells inhibiting inflammation, protects neurons from PANoptosis by downregulating REST[23]. Another study has indicated that by regulating the transformation of microglia from the M1 to the M2 phenotype, the neuronal death caused by PANoptosis can be effectively reduced[24]. This may be related to the downregulation of AIM2 and ZBP1 expression levels.

PANoptosis occurs in neurons during the subacute phase after ischemic stroke, exacerbating neuronal damage and death, and having an adverse effect on the recovery of neurological function. Directly targeting the components of the PANoptosome, such as AIM2 and ZBP1, to block the occurrence of PANoptosis can protect neurons from ischemia-reperfusion injury.

4.2 PANoptosis and sepsis associated encephalopathy

Sepsis is a severe systemic inflammatory response syndrome that often leads to multi-organ dysfunction, including damage to the central nervous system, manifested as sepsis-associated

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encephalopathy (SAE). SAE is characterized by the deterioration of mental status and cognitive function, but its pathological changes and mechanisms are not yet fully understood[25]. Studies have shown that PANoptosis is activated in SAE, involving multiple cell death programs such as pyroptosis, apoptosis, and necrosis[26]. Among these, apoptosis and pyroptosis are predominant, while necrosis plays a secondary role. Toll-like receptor 9 (TLR9) is an important regulator in the inflammatory response, and its expression is significantly increased in SAE. Further research indicates that TLR9 regulates PANoptosis by activating the p38 MAPK and ERK signaling pathways, and inhibiting TLR9 can significantly suppress the occurrence of PANoptosis and improve the survival rate and pathological changes in rats with SAE.

Sepsis is a severe inflammatory disease that triggers a cytokine storm, leading to multi-organ dysfunction, including damage to the central nervous system. Although there are currently few studies on PANoptosis in sepsis-associated encephalopathy, this field holds significant research value and potential clinical application prospects.

4.3 PANoptosis and Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of β-amyloid (Aβ) plaques and abnormal aggregation of Tau protein[27]. Neuroinflammation plays a significant role in the pathogenesis of AD, and PANoptosis, as an inflammatory mode of cell death, may be important in AD. Multiple cell death molecules in the PANoptosis pathway are activated in AD, leading to neuronal damage and death. For example, the activation of caspase-3 can lead to the cleavage of APP, thereby promoting the formation of Aβ plaques[28]. The activation of MLKL is associated with neuronal necrosis, further exacerbating neurodegenerative changes[29]. To some extent, PANoptosis can promote the clearance of Aβ plaques and tau protein through inflammatory responses. However, excessive inflammatory responses and cell death can exacerbate neuroinflammation and neuronal damage, leading to the worsening of AD. The release of inflammatory factors and the leakage of cellular contents caused by PANoptosis can further activate microglia and astrocytes, forming a vicious cycle that leads to the persistence and exacerbation of neuroinflammation. Moreover, AIM2 deficiency can reduce Aβ deposition and microglial activation in the 5xFAD mouse model, indicating that the AIM2-PANoptosome may play a role in AD[30].

In summary, PANoptosis plays a significant role in the pathological process of Alzheimer's disease by exacerbating inflammatory responses and promoting neuronal damage and death. A deeper understanding of the mechanisms by which PANoptosis operates in AD will aid in the development of new therapeutic strategies.

4.4 PANoptosis and glioma

Gliomas are the most common primary tumors of the central nervous system, characterized by high heterogeneity and variable survival rates[31]. Research has found that the expression levels of genes related to PANoptosomes in gliomas are significantly different from those in normal tissues[32]. These changes in gene expression may be closely related to the occurrence, development, and prognosis of gliomas. PANoptosis has strong immunogenicity, which can activate the immune system and promote the recognition and elimination of tumor cells by immune cells. Studies have shown that the activity of ZBP1 is regulated by ADAR1. ADAR1 interacts with the Zα2 domain of ZBP1, inhibiting ZBP1-mediated PANoptosis, thereby promoting the occurrence of tumors[33]. The expression and activity of PANoptosis-related genes are associated with the infiltration levels of immune cells such as dendritic cells, macrophages, and T cells, suggesting that PANoptosis can regulate the infiltration of immune cells in the tumor microenvironment[34]. In addition, the expression and activity of PANoptosis-related genes are correlated with the molecular characteristics of gliomas (such as PTEN mutations). These molecular characteristics can affect the invasiveness of tumors and their sensitivity to treatment, thereby influencing the prognosis of patients.

Studying the mechanisms of PANoptosis in gliomas helps to deepen the understanding of the occurrence and development process of gliomas, and provides new molecular markers and potential targets for the diagnosis and treatment of gliomas.

5. Conclusion

Maintaining the homeostatic balance of programmed cell death (PCD) is crucial for the maintenance

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of normal physiological functions in the body. Once this balance is disrupted, abnormal pathological states will occur in the body. PANoptosis is an emerging mode of cell death, which is activated when the body encounters danger signals such as pathogen infection, damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs). In this process, various protein sensors recognize these signals and promote the assembly of PANoptosome complexes through a series of signaling pathways, thereby activating multiple effector molecules to drive cell death. The occurrence of PANoptosis is the result of the synergistic action of multiple factors, reflecting the complex interactions and regulatory networks between different death pathways within the cell. When a certain cell death pathway is inhibited, other signaling pathways may be activated or enhanced to compensate and maintain the overall effect of cell death. Therefore, regulating the expression levels of these key proteins and the activity of signaling pathways provides potential strategies for precise modulation of PANoptosis.

This article systematically expounds the concept, characteristics, and the currently known core molecular regulatory modes of PANoptosis, summarizes its role and impact in neurological diseases, and aims to provide new ideas and theoretical support for the pathological basis research and clinical treatment of related diseases. Future research can consider the following aspects: How do various injurious or non-injurious factors induce the occurrence of PANoptosis in brain tissue? Can new therapeutic strategies be developed targeting the regulatory mechanisms of PANoptosome, where inhibiting its function can alleviate inflammatory diseases and enhancing its function can treat infectious diseases? Agonists and inhibitors of PANoptosis have not been reported yet, so are there any other key molecules?

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