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Review

The Mechanism of PANoptosis in Alzheimer's Disease: Exploring the Multiple Network Regulation of Cell Death

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder primarily affecting the geriatric population, characterized by progressive cognitive impairment and behavioral abnormalities. Due to the absence of effective disease-modifying therapies, AD imposes a substantial burden on patients and their families. The etiology and pathogenesis of AD have not been fully elucidated; multiple pathological alterations have been implicated, including the deposition of β-amyloid (Aβ) plaques, abnormal tau phosphorylation, and neuroinflammatory responses. These pathological changes contribute to neuronal damage, synaptic dysfunction, and neuronal death, ultimately leading to brain atrophy. Recent studies have identified PANoptosis as a critical regulatory mechanism of programmed cell death that influences the pathological progression of AD through multiple pathways, including modulation of Aβ plaque deposition and regulating neuroinflammatory responses. However, the precise mechanisms of these effects remain unclear. This review aims to comprehensively analyze recent research findings, focusing on the regulatory role of PANoptosis in AD, exploring the specific manifestations of the intricate network of cell death regulation in AD pathogenesis. By providing a systematic overview of emerging findings, this review offers new insights into the pathogenesis of AD and highlights potential directions for the development of targeted therapeutic strategies.

Keywords: PANoptosis; Alzheimer's disease; cell death; network mechanism

1. Introduction

With the accelerating global aging process, the incidence of neurodegenerative diseases has been rising significantly. Among them, Alzheimer's disease (AD) has become the most common form of dementia in the elderly, imposing a substantial burden on both society and families [1,2]. According to statistical data from the World Health Organization, the global number of AD patients is increasing by several million annually and is expected to continue rising in the coming decades. The clinical characteristics of AD primarily manifest as progressive decline in multiple cognitive and behavioral functions, including memory, orientation, and language abilities. This deterioration severely impairs patients' ability to perform daily activities independently, leading to a sharp decline in their quality of life [3]. Meanwhile, the long-term caregiving needs impose a substantial economic burden and psychological stress on patients' families, posing a significant challenge to healthcare resources. The pathogenesis of AD is highly complex, involving intricate interactions among genetic, environmental, and neurobiological factors. Despite extensive research efforts over the years, the pathogenesis of AD remains incompletely understood. This lack of clarity has resulted in the absence of effective therapeutic strategies in clinical practice. Currently available drugs, such as cholinesterase inhibitors (e.g., donepezil, galantamine) and N-Methyl-D-Aspartate (NMDA) receptor antagonists (e.g., memantine), can only provide symptomatic relief to a certain extent but fail to fundamentally halt disease progression [4]. Therefore, exploring the pathogenesis of AD and finding new therapeutic targets and strategies has become an important issue that urgently needs to be addressed in the field of neuroscience.

The study of cell death mechanisms has long been a central focus in the field of medicine. Over the past few decades, apoptosis and pyroptosis have garnered extensive attention and have been the subject of in-depth research. Apoptosis, also known as programmed cell death, is a genetically regulated and orderly cell death process that plays a crucial role in physiological and pathological processes, including multicellular organism development, tissue homeostasis, and immune defense [5]. Pyroptosis, on the other hand, which is mainly mediated by the activation of inflammatory bodies and plays a key role in infectious diseases and inflammatory related diseases [6]. In recent years, PANoptosis has emerged as a novel form of cell death, gradually attracting the attention of researchers. PANoptosis is an inflammatory form of programmed necrosis that integrates features of apoptosis, pyroptosis, and necroptosis. It is activated through the assembly of the PANoptosome protein complex [7,8]. Currently, the role of PANoptosis has been partially explored in various diseases, including cancer, autoimmune disorders, and infectious diseases, yielding significant research advancements [9,10].

However, the role of PANoptosis in AD, a neurodegenerative disorder, remains insufficiently explored. Therefore, investigating the function and underlying mechanisms of PANoptosis in AD is of paramount importance. This will help us to comprehensively and deeply understand the pathogenesis of AD from a new perspective, fill the gap in cell death mechanism research in this field, and reveal the intrinsic relationship between pan apoptosis and AD pathological processes. Furthermore, it is expected to provide a solid theoretical basis for the development of new treatment strategies for AD, bring more effective treatment methods for AD patients, and improve their clinical efficacy.

2. Cell Death Modes in AD

2.1 The Role of Apoptosis in AD

In the pathological process of AD, apoptosis, as a form of programmed cell death, has been extensively studied and is recognized as playing a crucial role in the disease's pathogenesis [11]. The study has shown that neuronal apoptosis occurs in the brains of AD patients, which is closely associated with multiple pathological factors [4]. Firstly, the accumulation of β-amyloid (Aβ) is one of the hallmark pathological features of AD. The aggregation of Aβ peptides leads to the formation of toxic plaques, which can induce neuronal apoptosis through multiple pathways. For instance, Aβ can elevate oxidative stress levels, activate intracellular stress signaling pathways, and subsequently trigger apoptotic signaling [12], Aβ-induced neuroinflammation may further exacerbate neuronal damage and apoptosis by promoting the release of pro-inflammatory cytokines [13], abnormal phosphorylation of tau protein is another key pathological mechanism in AD [14]. In the brains of AD patients, hyperphosphorylated tau protein forms neurofibrillary tangles (NFTs), disrupting the neuronal microtubule structure and intracellular transport system. These structural and functional abnormalities interfere with normal neuronal physiology, ultimately leading to apoptosis [15,16]. Additionally, apoptosis-related gene expression and protein alterations play a driving role in the pathological progression of AD. For example, mutations or abnormal expression of certain genes may lead to overactivation of apoptotic signaling pathways, thereby accelerating neuronal death [17]. These findings suggest that apoptosis in the pathological progression of AD is not merely a terminal event of cell death but may also serve as a critical pathological driver.

In a word, the mechanisms of apoptosis in AD are highly complex and multifaceted, involving Aβ accumulation, abnormal tau protein phosphorylation, and the activation of apoptotic signaling pathways. Further investigation into these mechanisms will enhance our understanding of AD pathogenesis and provide a theoretical foundation for the development of novel therapeutic strategies.

2.2 The Role of Pyroptosis in AD

Pyroptosis, as an inflammatory form of cell death, plays a significant role in the pathological progression of AD. Recent studies have shown that Aβ deposition and abnormal tau protein phosphorylation in the brains of AD patients can activate inflammatory responses, thereby triggering pyroptosis [18,19]. During the process of pyroptosis, cells release various inflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-18 (IL-18), which further exacerbate neuroinflammation and neuronal damage [20]. Specifically, Aβ deposition and abnormal tau protein aggregation can activate the NOD-like receptor family protein 3 (NLRP3) inflammasome in microglia, subsequently leading to the activation of caspase-1. Activated caspase-1 cleaves gasdermin D (GSDMD), resulting in the formation of membrane pores and the initiation of pyroptosis [21]. This process not only exacerbates neuroinflammation but also amplifies inflammatory signaling through the release of pro-inflammatory cytokines, ultimately causing further neuronal damage and death [22]. Additionally, studies have revealed that pyroptosis-related signaling pathways and molecules exhibit abnormal expression in the brains of AD patients. For example, activation of the NF-κB signaling pathway can enhance the expression of the NLRP3 inflammasome, promote the release of inflammatory cytokines, and thereby exacerbate the pathological progression of AD [23]. This abnormal form of cell death may interact with the pathological mechanisms of Aβ and tau protein, forming a vicious cycle that further drives the progression of AD.

This shows, pyroptosis plays a significant role in the pathological progression of AD. Its interaction with Aβ deposition and abnormal tau protein aggregation presents a potential therapeutic target for future AD interventions.

2.3 The Role of Necroptosis in AD

In the pathological process of AD, necroptosis, as a regulated form of cell death, has been demonstrated to play a crucial role. Under the influence of various stress factors, neurons in the brains of AD patients activate the necrotic apoptotic signaling pathway. This process is primarily mediated by Receptor-interacting protein kinase 1 (RIPK1), Receptor-interacting protein kinase 3 (RIPK3), and the pseudokinase Mixed lineage kinase domain-like protein (MLKL). Ultimately, it leads to cell membrane rupture, the release of cellular contents, and the subsequent induction of inflammatory responses and tissue damage [24]. Recent studies have further elucidated the specific mechanisms of necroptosis in AD. For example, abnormal tau protein phosphorylation has been identified as a key trigger of necroptosis [24] AD mouse models, the presence of tau pathology has been shown to significantly activate necroptosis, whereas this activation is not observed in models expressing only Aβ pathology [25]. Additionally, a study by Yang *et al.* [26] found that the necroptosis inhibitor

Necrostatin-1 (Nec-1) could block Aβ-induced cell death in Amyloid Precursor Protein/Presenilin-1 (APP/PS1) transgenic mice. In AD, potential genetic targets of necroptosis are gradually being identified. In vivo studies suggest that targeting these molecules can effectively ameliorate cognitive impairment in AD animal models [25]. For example, MLKL gene knockout has been shown to significantly impair cognitive function, learning, and memory in AD mouse models [27].

The occurrence of necroptosis not only exacerbates neuronal damage but also further promotes the development of neuroinflammation by releasing inflammatory factors [28,29]. This inflammatory response interacts with Aβ deposition and abnormal tau protein aggregation, forming a vicious cycle that further accelerates the pathological progression of AD [30]. Additionally, activation of the NF-κB signaling pathway may play a key role in this process by enhancing the expression of inflammatory cytokines, thereby further exacerbating neuroinflammation [30].

Therefore, necroptosis plays a crucial role in the pathological mechanisms of AD, and its interaction with Aβ deposition and abnormal tau protein aggregation presents new potential therapeutic targets for AD treatment. Research will further explore the specific mechanisms of necroptosis in AD and evaluate its feasibility and safety as a therapeutic target.

2.4 The Crosstalk and Regulatory Interactions Among Apoptosis, Pyroptosis, and Necroptosis

In AD research, the crosstalk and regulatory interactions among apoptosis, pyroptosis, and necroptosis have garnered extensive attention from research teams. The emerging study continues to reveal the complex roles of these cell death mechanisms in disease progression [31]. For instance, Caspase-8 acts as a pivotal regulatory factor in cell death, functioning as a cellular compass to facilitate apoptosis, necroptosis, or pyroptosis based on its post-translational modifications and the specific cell type involved. Moreover, Majerníková *et al*. [32] discovered that the abnormal accumulation of Aβ and tau protein in the brains of AD patients not only triggers the conventional apoptotic process but is also closely associated with the activation of ferroptosis pathways. In their experiment, researchers used transgenic mouse models to simulate Aβ plaque formation and found that Aβ accumulation in neurons enhances NLRP3 inflammasome activation, thereby triggering pyroptotic responses. Moreover, this process accelerates neurodegenerative damage within the inflammatory microenvironment [33]. Additionally, Dong *et al*. [25] further confirmed in mouse models the close relationship between tau protein phosphorylation and neuronal necroptosis. Some research teams have also observed that in tau gene mutation-induced mouse models, neurons exhibit early-stage energy metabolism disturbances and cell membrane damage, ultimately leading to necroptotic cell death [34]. Abnormal phosphorylation of tau protein destabilizes the microtubule structure, leading to mitochondrial dysfunction and the release of large amounts of cytokines, ultimately triggering necroptosis [35]. Regarding the role of inflammation, Zhu *et al*. [36] conducted a Mendelian randomization study, revealing how chronic inflammatory responses in AD regulate both apoptosis and pyroptosis through a dua. Feng *et al*. [23] discovered that inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) not only activate Cysteine-dependent aspartate-specific protease-3 (caspase-3) through the classical apoptotic pathway but also promote NLRP3 inflammasome assembly, thereby indu. Furthermoresis. Furthermore, by using anti-TNF-α antibodies, they successfully reduced neuronal death in mouse models. Additionally, NLRP3 gene knockout significantly suppressed the pyroptotic response, further demonstrating the critical role of inflammation in regulating cell death [22]. Yang *et al*. [26] reported that the SUMOylation modification of the Tumor Protein p53 (p53) is associated with the pathological mechanisms of AD, potentially accelerating cellular senescence and tau protein pathology [37]. This study, through proteomic analysis, identified cell death-related pathways in AD, including the upregulation of p53 protein and its potential role in multiple cell death mechanisms.

These studies provide critical experimental evidence, demonstrating that the crosstalk and regulatory interactions among apoptosis, pyroptosis, and necroptosis in AD are not merely theoretical hypotheses. Key pathological factors such as Aβ, tau, inflammatory factors, and mitochondrial damage also interact with each other. The studies have explored the interactions among neurodegeneration, immune response, and cell death, presenting the PANoptosis regulatory network in AD (Fig. 1). In the future, through extensive investigations by different research teams, the complex interplay among these cell death mechanisms is being progressively unveiled. A deeper understanding of these interactions will enhance our comprehension of AD pathogenesis and offer new research directions for future targeted therapeutic interventions.

3. The Association Between PANoptosis and Pathological Changes in AD

3.1 Concept of PANoptosis and PANoptosome

PANoptosis is a unique form of regulated inflammatory cell death mediated by PANoptosomes, a concept first proposed by Malireddi *et al*. [38]. In 2019, this phenomenon was described as a cell death mechanism that cannot be fully explained by any single traditional programmed cell death pathway [38]. PANoptosomes, a multi - protein complex serving as the molecular platform for PANoptosis, integrate key molecules from three programmed cell death pathways—pyroptosis, apoptosis, and necroptosis—forming a shared activation platform. Depending on their functions, PANoptosomes consist of specific sensors (e.g.,

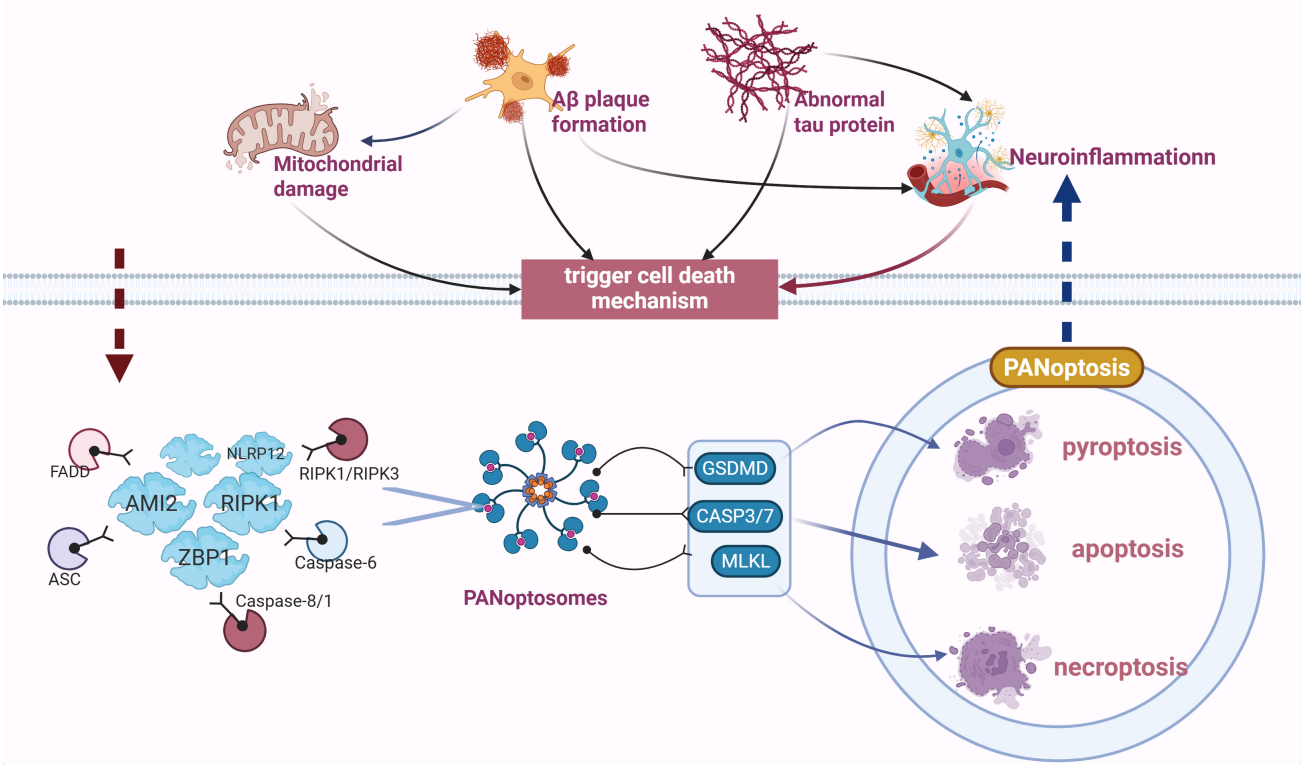

Fig. 1. PANoptosis regulatory network in Alzheimer's disease (AD). This study first reveals the interconnections and mutual influences among four core pathological factors in AD — β-amyloid (Aβ) plaque formation, abnormal tau protein, inflammatory response, and mitochondrial damage — which collectively trigger cell death mechanisms. Secondly, it demonstrates the PANoptosis regulatory network in AD: when neurons are stimulated by Aβ, tau protein, inflammatory factors, and mitochondrial damage, they induce PANoptosome formation. This platform coordinates the interactions and regulation among pyroptosis, apoptosis, and necroptosis, ultimately leading to neuronal death. The resulting neuronal death further exacerbates inflammatory responses, creating a vicious cycle. FADD, Fas-associated via death domain; ASC, apoptosisassociated speck-like protein containing a CARD; AMI2, AIM2-like receptor 2; RIPK1, Receptor-Interacting Protein Kinase 1; NLRP12, NACHT, LRR and PYD domains-containing protein 12; RIPK3, Receptor-Interacting Protein Kinase 3.

Z-DNA binding protein 1 (ZBP1), RIPK1, Interferon-inducible protein AIM2 (AIM2)), adapters (e.g., apoptosis-associated speck-like protein containing a CARD (ASC), Fas-associated via death domain (FADD)), and effectors (e.g., RIPK1, RIPK3, caspase-8, caspase-1). Their assembly is triggered by upstream signals, ultimately leading to lysosomal cell death. Based on their distinct characteristics, we have identified PANoptosis-related molecules and their potential therapeutic value in AD (Table 1).

Firstly, as one of the sensors, ZBP1 functions as an innate immune receptor capable of recognizing Z-shaped nucleic acid (Z-DNA) structures generated by viruses or hosts. This recognition activates immune signaling pathways and regulates cell death and inflammatory responses. The hallmarks of ZBP1-PANoptosome include the activation of Caspase-1, Caspase-3, Caspase-8, and the phosphorylation of MLKL. Studies have demonstrated that when stimulated by Influenza A Virus (IVA), ZBP1 is activated as a specific recognition receptor, triggering the assembly of PANoptosome complexes [39,40], ZBP1 also induces necroptosis by activating the RIPK3-MLKL signaling axis (RIPK3 phosphorylates MLKL, which damages the cell membrane) [41], the RIPK1-PANoptosome is mainly composed of RIPK1, ASC, Caspase-1, Caspase-8, and fas-associated protein with death domain (FADD). Professor Malireddi's team [38] found that the deletion or functional inactivation of the TAK1 gene can trigger the assembly of the RIPK1-PAnoptosome, which can serve as the main regulatory switch of the RIPK1-PANoptosome [38] has shown that in the TNF/TNF receptor 1 (TNFR1) signaling pathway, RIPK1 activates the NF-κB pathway through ubiquitination, promoting cell survival. When deubiquitination occurs, RIPK1 forms a complex with FADD and Caspase-8, triggering apoptosis or necroptosis [28,42,43] addition, the constituent molecules of AIM2-PANoptosome include AIM2, ZBP1, pyrin, ASC, Caspase-1, Caspase-8, RIPK1, RIPK3, and FADD [44]. The AIM2 inflammasome can sense double-stranded DNA. AIM2 drives inflammatory signal transduction and inflammatory cell apoptosis by regulating the innate immune sensors Pyrin and ZBP1, which

Table 1. PANoptosis-related molecules and their potential therapeutic value in AD.

Molecules	Mechanism	Pathological significance	Therapeutic value
ZBP1	Perceive Z-DNA to activate pan-apoptosis	ZBP1 inhibitors; Traditional Chinese medicine intervention	Medium risk, further study and verification are required
RIPK1	The RIPK1/RIPK3/MLKL complex is activated through the TNF-α signaling pathway	RIPK1 inhibitors (Nec-1, GSK-872); Traditional Chinese medicine intervention	High risk, but research has shown its therapeutic potential
RIPK3	Forming a complex with RIPK1 to recruit MLKL	RIPK3 inhibitor (GSK'2118436); Traditional Chinese medicine intervention	Medium risk, further study and verification are required
AIM2	The RIPK1/3 complex releases mitochondrial DNA (mtDNA) and activates inflammatory caspases	Indirect regulation by NLRP3 inhibitors; intervention with traditional Chinese medicine	Low risk, but limited research; requires further verification of its direct association with AD
ASC	Serves as an adapter protein that bridges NLRP3 and caspase-1	Angiotensin-converting enzyme inhibitors; Traditional Chinese medicine intervention	High risk, further study is needed
FADD	Interacts with RIPK1 to form the death-inducing signaling complex (DISC)	No specific inhibitor exists	Low risk, but little research
Caspase-1	Activated by NLRP3 inflammasome, it cleaves IL-1β and IL-18 precursors, thereby inducing pyroptosis	Caspase-1 inhibitor (VX-765); Traditional Chinese medicine intervention	Moderate risk, supported by animal studies
Caspase-3	Activated by Aβ oligomers, it participates in neuronal apoptosis	Caspase-3 inhibitors (Z-VAD-FMK, IDN-6556); Traditional Chinese medicine intervention	High risk, treatment strategies need to be carefully designed
Caspase-8	Interacts with RIPK1 to regulate necroptosis; may be involved in pyroptosis	Caspase-8 inhibitor (Z-IETD-FMK); Traditional Chinese medicine intervention	Moderate risk, supported by some animal studies
NLRP3	Identify Aβ oligomers and tau protein aggregates, then recruit ASC and caspase-1 to form a complex	NLRP3 inhibitors (MCC950, BMS-986020); Traditional Chinese medicine intervention	Moderate risk, requiring balance between anti-inflammatory and immunomodulatory effects; supported by clinical trials
ADAR1	Inhibit ZBP1-mediated apoptosis	ADAR1 activator; Traditional Chinese medicine intervention	Low risk, but little research
TAK1	Upstream regulation of RIPK1 activity	TAK1 inhibitors; Traditional Chinese medicine intervention	Low risk, but little research

ZBP1, Z-DNA binding protein 1; Z-DNA, Z-shaped nucleic acid; RIPK1, Receptor-interacting protein kinase 1; RIPK3, Receptor-interacting protein kinase 3; MLKL, Mixed lineage kinase domain - like protein; TNF-α, Tumor Necrosis Factor-alpha; Nec-1, Necrostatin-1; AIM2, Interferon-inducible protein AIM2; ASC, apoptosis-associated speck-like protein containing a CARD; FADD, Fas-associated via death domain; IL-1β, Interleukin-1β; IL-18, Interleukin-18; Caspase-1, Cysteine-dependent aspartate-specific protease-1; Caspase-3, Cysteine-dependent aspartate-specific protease-3; Caspase-8, Cysteine-dependent aspartate-specific protease-8; NLRP3, NOD-like receptor family protein 3; ADAR1, Adenosine deaminase acting on RNA 1; TAK1, Transforming growth factor beta-activated kinase 1.

plays an important role in normal human development, infectious diseases, inflammation, and tumors.

In addition to the above, studies have also found that NLR family pyrin domain containing 12 (NLRP12) drives the activation of inflammasomes and PANoptosomes, cell death, and inflammation in response to heme plus pathogen-associated molecular patterns (PAMPs) or TNF. Toll-like receptor 2/4 (TLR2/4) induces NLRP12 expression via the Interferon Regulatory Factor 1 (IRF1)-mediated signaling pathway, leading to the formation of inflammasomes and subsequently inducing the maturation of IL-1β and IL-18. The inflammasome also serves as an important component of the NLRP12-PANoptosome, driving inflammatory cell death via caspase-8/RIPK3 [45]. Moreover, the research team led by Sundaram *et al.* [46] demonstrated through experiments that the TLR signaling pathway and Nicotinamide adenine dinucleotide (oxidized form) levels regulate the expression of NLR family, CARD domain containing 5 (NLRC5) and the production of Reactive Oxygen Species (ROS), thus controlling cell death.

PANoptosis is closely associated with various diseases, including infectious diseases, cancer, neurodegen-

erative disorders, and cardiovascular diseases. Due to its highly pro-inflammatory nature, PANoptosis plays a crucial role in the onset and progression of diseases, making it a potential therapeutic target.

3.2 Aβ Deposition and PANoptosis

Aβ deposition is one of the core pathological changes in AD, and its role in the neurodegenerative process has been increasingly recognized [47]. The accumulation of Aβ is not only closely associated with cognitive decline but also induces multiple pathological changes within cells through various signaling pathways, ultimately leading to PANoptosis [48,49].

Firstly, Aβ induces oxidative stress and promotes the generation of reactive ROS, disrupting intracellular homeostasis and causing damage to the cell membrane, mitochondria, and DNA [50]. Oxidative stress-induced free radical reactions not only directly damage cellular structures but also activate multiple stress signaling pathways, further promoting cell death [51]. Studies have shown that Aβ can regulate the expression of antioxidant enzymes by activating the Nuclear factor erythroid 2-related factor 2-Antioxidant response element (Nrf2-ARE) signaling pathway. However, dysregulation of this process often leads to a reduced cellular response to oxidative damage, thereby promoting PANoptosis [52]. Additionally, Aβ disrupts intracellular calcium homeostasis [52], inducing endoplasmic reticulum stress and mitochondrial dysfunction [53]. Under the accumulation of Aβ, intracellular calciumion concentration increases, which not only disrupts normal intracellular signaling pathways but also causes a decrease in mitochondrial membrane potential, leading to impaired Adenosine Triphosphate (ATP) synthesis. This, in turn, triggers mitochondria-mediated apoptosis and necroptosis [54,55]. Studies have shown that Aβ deposition can activate calcium-dependent enzymes, such as calcium/calmodulin-dependent protein kinase II (CaMKII), thereby regulating cell death pathways [56]. During this process, cells release cytokines, as well as pro-apoptotic factors such as cytochrome c and Second Mitochondria-derived Activator of Caspases (Smac/DIABLO), which promote the activation of apoptotic signaling, further exacerbating neuronal loss [52]. In terms of inflammatory response, Aβ deposition can also exacerbate local neuroinflammation by activating the immune response of microglia and astrocytes [57]. These immune cells secrete cytokines such as TNF-α, IL-1β, and Interleukin-6(I) and, activating signaling pathways such as NF-κB and Mitogen-Activated Protein Kinase (MAPK), thereby exposing neurons to a sustained inflammatory state [58]. The study has shown that the elevation of inflammatory cytokines can simultaneously stimulate apoptosis and pyroptosis, leading to further neuronal damage [59]. Microglia play a protective role by clearing Aβ plaques. However, when overactivated, they shift to a pro-inflammatory phenotype, releasing excessive inflammatory cytokines, ultimately leading to apoptosis and necrosis [60,61]. Aβ deposition may further exacerbate cellular damage by interacting with various molecules and signaling pathways associated with PANoptosis. For example, Aβ accumulation is closely associated with the activation of stress response factors such as p53, p38, JNK and MAPK. These factors not only regulate cell cycle progression and DNA repair but also play a crucial role in cell death decision-making processes [62]. Under the influence of Aβ, the aberrant activation of these signaling pathways often drives cells into irreversible damage under stress conditions, thereby initiating multiple cell death pathways and ultimately accelerating the progression of neurodegeneration [63]. Additionally, Aβ interacts extensively with various apoptosis-related factors within the cell, such as the B-cell lymphoma/leukemia-2 (BCL-2) genefamily proteins and caspases [64].

Studies have shown that Aβ can downregulate the expression of the anti-apoptotic factor BCL-2 while upregulating the pro-apoptotic factor Bax, thereby triggering the mitochondrial apoptotic pathway and promoting cell death [65]. At the same time, Aβ can impair the proteasomal system, disrupting protein degradation within the cell, further exacerbating cellular stress responses and promoting cell death.

Thus, Aβ accumulation disrupts multiple intracellular signaling pathways not only by inducing oxidative stress, disrupting calcium homeostasis, and activating inflammatory responses, but also by interacting with PANoptosis-related molecules and signaling networks, thereby exacerbating neuronal damage and death. A deeper exploration of the relationship between Aβ deposition and PANoptosis will enhance our comprehensive understanding of AD pathogenesis and provide a theoretical foundation for the development of novel therapeutic strategies for the disease.

3.3 Abnormal Tau Protein and PANoptosis

Abnormal tau protein is another key pathological change in AD, and its role in neuronal damage has become a major focus in neuroscience research [66]. Tau protein primarily stabilizes the microtubule network, maintaining neuronal structural integrity and function [67]. Recent studies have shown that abnormal tau protein is closely associated with PANoptosis, involving multiple cell death pathways, including apoptosis, pyroptosis, and necroptosis. These different forms of cell death exhibit a complex, interwoven, and mutually reinforcing relationship in the pathological process of AD [68].

Firstly, excessive phosphorylation of tau protein alters its structure, leading to the aggregation of tau fibrils and the formation of NFTs. These aggregated tau proteins not only disrupt microtubule stability but also interfere with intracellular transport and cytoskeletal organization, ultimately resulting in neuronal dysfunction [69]. Studies have also found that abnormal tau protein aggregation leads to mitochondrial membrane potential loss, impaired ATP synthe-

sis, and disrupted mitochondrial dynamics, resulting in mitochondrial dysfunction. These changes cause intracellular calcium accumulation, triggering cellular stress responses, including endoplasmic reticulum (ER) stress and oxidative stress. Consequently, these stress signals activate cell death pathways, ultimately leading to PANoptosis [70].

Abnormal tau protein aggregation activates intracellular stress-related signaling pathways, such as JNK, p38 MAPK, and ERK, thereby initiating a series of molecular events associated with PANoptosis [71]. Abnormal tau aggregation not only upregulates pro-apoptotic molecules such as Bax and p53 but also downregulates anti-apoptotic molecules such as BCL-2, leading to the activation of the mitochondrial pathway and the initiation of apoptosis [72]. Further studies have also suggested that tau aggregation can disrupt normal autophagic flux, preventing cells from efficiently removing damaged organelles and proteins under metabolic stress, thereby further exacerbating cell death [73].

Additionally, abnormal tau interacts with neuronal autophagy pathways, regulating autophagy-mediated neuronal death through the classical apoptotic pathway [74] tau may also contribute to the neurodegenerative process of AD through non-classical cell death pathways, such as pyroptosis and necroptosis [75]. For example, studies have shown that abnormal tau accumulation can induce necroptosis by activating the RIPK1/RIPK3 signaling pathway. This pathway is activated when cells are exposed to damage, leading to cell membrane rupture and the release of intracellular contents, which in turn exacerbates inflammation and further damages neural tissue [76,77]. Additionally, abnormal tau may promote pyroptosis by activating the NLRP3 inflammasome.

Function, leading to the accumulation of abnormal proteins within the cell, which in turn activates intrinsic stress responses and induces cell death [78]. Additionally, tau interacts with key signaling pathways, including protein kinase B (AKT)/mTOR, P53, and BCL-2 family proteins. Dysregulation of these pathways may disrupt the balance between cell survival and death, ultimately accelerating the occurrence of PANoptosis [79,80].

In summary, the abnormal tau protein affects neuronal survival not only through the classical apoptotic pathway but also induces various forms of cell death by broadly activating PANoptosis-related signaling molecules. An in-depth investigation into the relationship between abnormal tau and PANoptosis holds significant theoretical value and clinical relevance for elucidating the pathological mechanisms of AD and identifying potential therapeutic targets.

3.4 The Role of Inflammatory Response in PANoptosis

One of the pathological characteristics of AD is the continuous inflammatory response among neurons. This response not only directly activates immune cells, triggering local neuroinflammation, but also promotes cell death, particularly PANoptosis, via multiple signaling pathways [81,82]. The activation of inflammatory response. Theretoreically accompanied by the release of inflammatory cytokines, such as IL-1β, tumor necrosis TNF-α, and IL-6matory cytokines influence PANoptosis through multiple direct and indirect pathways. Firstly, these cytokines can directly induce PANo. Inflammatory stimuli activate specific receptors and signaling pathways. For instance, TNF-α, upon binding to TNFR1, activates the death receptor signaling pathway (e.g., Death Receptor 3, Death Receptor 4), subsequently triggering the activation of caspase family members, such as caspase-8, thereby initiating the apoptotic process [52], TNF-α activates the NF-κB signaling pathway, promoting the further release of inflammatory cytokines, thereby creating a vicious cycle of inflammation and exacerbating neuronal damage. Therefore, IL-1β, a pro-inflammatory cytokine, also plays a crucial role in the process of PANoptosis [83]. Studies have shown that IL-1. Additionallye the NLRP3 inflammasome, initiating inflammation-mediated cell death, specifically pyroptosis. Therefore, IL-1β not only exacerbates neuronal damage through conventio. Excessivematory pathways but may also promote neuronal death by inducing pyroptosis. Additionally, inflammatory cytokines indirectly promote PANoptosis by influencing intracellular oxidati. Atstress levels and mitochondrial function. Inflammatory cytokines such as TNF-α and IL-1β can induce the production of react. Excessive activating enzymes like NADPH oxidase (NOX). ROS not only directly damages cell membranes, proteins, and DNA, but also disrupts intracellular antioxidant systems, further exacerbating oxidative stress within the cell [84]. Excessive accumulation of oxidative stress not only disrupts various cellular functions but also promotes cell death by activating signa. Autophagyays such as p53, JNK, and p38 MAPK [85,86]. Meanwhile, oxidative stress and inflammatory cytokines not only significantly affect mitochondrial function, but also activate mitochondrial-associated signaling pathways. For example, ROS-induced damage to the mitochondrial inner membrane leads to the loss of mitochondrial membrane potential, which in turn triggers mitochondria-mediated cell death [87,88] release of Cytochrome c (Cyt-c), Smac/DIABLO, and other mitochondrial molecules further activates caspase family members, initiating the apoptotic process [89]. As mitochondrial function deteriorates, the cell's ATP synthesis capacity declines, resulting in insufficient energy supply, eventually leading the cell into an irreparable death state [87,90]. Moreover, inflammatory cytokines indirectly promote PANoptosis by affecting the cellular autophagy process [91] is a crucial process for cellular self-clearance of damaged components and the maintenance of homeostasis. However, in AD, the prolonged influence of inflammatory cytokines often leads to autophagy dysregulation [92] have found that overactivated inflammatory cytokines may inhibit autophagic flux or disrupt autophagosome fusion, pre-

venting cells from effectively clearing damaged organelles and proteins. This exacerbates intracellular damage and ultimately induces PANoptosis [93,94].

Thus, inflammatory cytokines not only directly promote cell death by activating PANoptosis-related signaling pathways but also play a crucial role in PANoptosis through indirect mechanisms, such as oxidative stress, mitochondrial dysfunction, and dysregulation of autophagy. The sustained activation of inflammatory cytokines forms a vicious cycle in the pathological progression of AD: the release of inflammatory cytokines promotes neuronal death, while neuronal death further exacerbates inflammation, thereby accelerating disease progression. Therefore, targeting inflammatory cytokines and their associated signaling pathways may serve as a promising therapeutic strategy for AD treatment in the future.

In summary, PANoptosis is closely associated with neurodegeneration in AD, particularly in the context of Aβ deposition, abnormal tau protein aggregation, inflammatory responses and mitochondrial damage.

4. Potential Therapeutic Targets and Drug Development for PANoptosis in Alzheimer's Disease

The role of PANoptosis in AD is complex and multidimensional. Therefore, its potential therapeutic targets exhibit remarkable diversity and multidimensional characteristics, spanning multiple levels, including PANoptosome core proteins, upstream activation signals, and downstream signaling pathways. Depending on their different characteristics, different potential therapeutic values can be explored (Table 1).

Firstly, the core proteins and signaling pathways involved in PANoptosis provide potential therapeutic targets for drug development. For example, caspase family members, particularly caspase-3 and caspase-8, play a key role in the classical apoptotic process. They not only induce cell death by cleaving intracellular substrates but also regulate inflammatory responses and cytokine release, thereby indirectly promoting PANoptosis [95] have indicated that caspase inhibitors may exert neuroprotective effects against neuronal death in AD. Specifically, caspase-3 shows considerable activation in AD models, and blocking its activity can significantly mitigate Aβ-induced neuronal damage and cognitive impairment [96] caspase inhibitors may serve as a promising strategy to slow the progression of AD. Beyond caspases, inflammatory cytokines such as TNF-α and IL-1β are also key regulatory molecules in the PANoptosis process [36]. In the pathological state of AD, these inflammatory cytokines promote a vicious cycle of neuroinflammation by activating signaling pathways such as NF-κB, MAPK, and JNK. Additionally, they induce apoptosis and pyroptosis by activating death receptors such as TNFR1 [97,98], inhibiting these inflammatory cytokines or their receptors may not only alleviate neuroinflammation but also reduce the occurrence of PANoptosis.

In recent years, monoclonal antibodies and small-molecule inhibitors targeting TNF-α and IL-1β have entered clinical trial stages, demonstrating promising potential and offering new hope for AD treatment [99,100] important therapeutic target is the NLRP3 inflammasome, whose role in PANoptosis has been increasingly recognized [101]. The NLRP3 inflammasome not only plays a central role in the inflammatory response but is also closely associated with the induction of pyroptosis and necroptosis [102]. Therefore, inhibiting NLRP3 inflammasome activation or its downstream signaling pathways, such as those involving caspase-1, may serve as an effective strategy for intervening in PANoptosis.

In addition to these direct regulators of PANoptosis, mitochondrial function and its associated regulatory factors offer a wealth of potential therapeutic targets. Experimental studies have demonstrated that baicalin inhibits PANoptosis in macrophages by blocking mitochondrial Z-DNA formation and ZBP1-PANoptosome assembly, thereby protecting against inflammatory diseases [103], BCL-2 family proteins, such as BCL-2 and Bax, play a critical role in regulating the mitochondrial apoptotic pathway [104,105] modulating the BCL-2/Bax ratio or directly targeting these proteins with pharmacological interventions, it may be possible to restore apoptotic balance and slow down neuronal death in AD. Additionally, autophagy, an important cellular self-protection mechanism, is closely linked to PANoptosis. In AD, autophagic flux dysregulation can lead to the accumulation of toxic substances within the cell, thereby exacerbating cellular damage [106,107] modulating autophagy-related molecules such as mTOR and Beclin-1, it may be possible to restore the cell's ability to clear damaged components, thereby alleviating neurodegenerative lesions [108,109]. Drugs targeting autophagy regulatory molecules have made significant progress in the preclinical stage [110] and they may provide new therapeutic options for the treatment of AD in the future.

In addition to molecular targets, therapeutic strategies for PANoptosis also include regulating oxidative stress and restoring calcium homeostasis, which are crucial for maintaining intracellular environmental balance [111,112] such as vitamin E and alpha-lipoic acid have been used in clinical trials for various neurodegenerative diseases. Although the effects have been limited, oxidative stress control remains a promising therapeutic direction [113,114]. The use of calcium channel antagonists and their analogs helps to reduce the activation of calcium-dependent enzymes, thereby alleviating intracellular toxic responses [115].

The multiple signaling pathways and molecules involved in PANoptosis provide abundant therapeutic targets for AD treatment. By conducting in-depth research into the molecular mechanisms of PANoptosis and developing

drugs or interventions targeting these key molecules, we can not only slow down the pathological progression of AD but also effectively protect neurons and alleviate neurodegenerative lesions. As our understanding of PANoptosis mechanisms deepens, we are likely to develop more precise and effective therapies, offering new hope for AD patients.

Although the development of PANoptosis-targeting drugs shows great promise, there are still many challenges in the research and development process. First, drug safety is a significant concern. AD patients often have multiple comorbidities, such as cardiovascular diseases and diabetes, so drugs targeting PANoptosis must consider potential drug interactions and possible side effects. Second, the efficacy and specificity of these drugs need further validation. Since PANoptosis involves multiple signaling pathways and forms of cell death, precisely selecting targets and achieving specific regulation while avoiding damage to normal and off-target cells remains a major challenge in drug development. As AD is a chronic, progressive neurodegenerative disease, the timing and duration of drug treatment are crucial. Therefore, the long-term effects and tolerability of these drugs need to be thoroughly evaluated in clinical trials. In conclusion, the development of PANoptosis-targeting drugs holds the potential to provide new breakthroughs in the treatment of AD.

5. Current Challenges and Controversies

Current research on PANoptosis in AD encounters several controversies:

First, the specific assembly mechanism of PANoptosome complexes in AD brains remains unclear. Different studies have shown discrepancies in the interactions between core components (such as ZBP1 and AIM2). Second, the causal relationship between PANoptosis and traditional cell-death pathways (apoptosis/pyroptosis/necroptosis) has not been clarified. Some studies suggest that it is an independent regulatory mechanism, while other evidence supports the idea that it may be a synergistic effect under stress conditions. For example, TAK1 kinase inactivation can both induce RIPK1-dependent PANoptosome assembly and activate the independent RIPK3-MLKL necroptotic pathway. Additionally, existing animal models cannot fully simulate the spatiotemporal dynamics of PANoptosis in AD patient brains, which limits their clinical translational value. Although the IAV infection model can activate the ZBP1-PANoptosome, it cannot reproduce the regulatory effects of AD's characteristic Aβ-tau pathological microenvironment on cell-death networks.

Moreover, current research faces multiple challenges: At the experimental technical level, the dynamic assembly process of the PANoptosome complex is difficult to monitor in real time, and the spatial resolution of existing super-resolution microscopy techniques in tissue samples is still unable to capture transient protein interactions. In terms of mechanism analysis, the cross-regulation of multiple signaling pathways increases the complexity of the mechanism. For example, the NF-κB pathway is involved in both inflammation activation and cell survival regulation, making it difficult to clarify its primary and secondary roles in PANoptosis. In terms of clinical translation, the blood-brain barrier limits the penetration of macromolecular drugs. Although the latest research shows that nanocarrier delivery systems can effectively mediate drug crossing of the Blood-Brain Barrier (BBB) to achieve brain enrichment, the vast majority of studies have not effectively quantified the efficiency of drug crossing of the blood-brain barrier, especially ignoring the impact of blood-brain barrier changes under physiological and pathological conditions on the ability of nanocarrier delivery systems to cross the BBB. In addition, existing short-term intervention models cannot simulate the chronic progression characteristics of human AD.

6. Conclusion

PANoptosis plays an important role in the onset and progression of AD. It is involved in the pathological processes of AD through various mechanisms, such as affecting neuronal survival and function, and promoting the onset of neuroinflammation. However, there are still some differences in the specific roles and mechanisms of PANoptosis in AD across different studies. Future research needs to further clarify the precise mechanisms of PANoptosis in AD to better understand the disease's pathogenesis. At the same time, there should be an increased focus on studying PANoptosis-related signaling pathways to explore potential therapeutic targets. Moreover, conducting interdisciplinary research and combining basic research with clinical practice will help drive the development of treatment methods for AD. In conclusion, the role and mechanisms of in AD are complex but of significant research importance. Future studies need to integrate different perspectives and findings to advance this field and provide new insights and methods for AD treatment.

Abbreviations

AD, Alzheimer's disease; Aβ, β-amyloid; IL-1β, Interleukin-1β; IL-18, Interleukin-18; GSDMD, Gasdermin D; RIPK1, Receptor-interacting protein kinase 1; RIPK3, Receptor-interacting protein kinase 3; MLKL, Mixed lineage kinase domain-like protein; Nec-1, Necrostatin-1; NLRP3, NOD-like receptor family protein 3; TNF-α, Tumor Necrosis Factor-alpha; Caspase-3, Cysteine-dependent aspartate-specific protease-3; ROS, Reactive Oxygen Species; Nrf2-ARE, Nuclear factor erythroid 2-related factor 2-Antioxidant response element; CAMKII, calcium/calmodulin-dependent protein kinase II; Cyt-c, Cytochrome c; IL-6, Interleukin-6; MAPK, Mitogen-Activated Protein Kinase; BCL-2, B-cell lymphoma/leukemia-2 gene; NFTs, neurofibrillary tangles; AKT, Protein Kinase B; P53, Tumor Protein p53; TNFR1, TNF receptor 1; NOX, NADPH oxidase; ZBP1, Z-DNA

binding protein 1; AIM2, Interferon-inducible protein AIM2; ASC, apoptosis-associated speck-like protein containing a CARD; FADD, Fas-associated via death domain; Caspase-1, Cysteine-dependent aspartate-specific protease-1; Caspase-8, Cysteine-dependent aspartate-specific protease-8; ADAR1, Adenosine deaminase acting on RNA 1; TAK1, Transforming growth factor beta-activated kinase 1; IVA, Influenza A virus; NLRP12, NLR family pyrin domain containing 12; TLR2/4, Toll-like receptor 2/4; IRF1, Interferon Regulatory Factor 1; NLRC5, NLR family, CARD domain containing 5; Smac/DIABLO, Second Mitochondria-derived Activator of Caspases; BBB, Blood-Brain Barrier; NMDA, N-Methyl-D-Aspartate; APP/PS1, Amyloid Precursor Protein/Presenilin-1; ER, Endoplasmic Reticulum.

Author Contributions

HW & BCW conceptualized the manuscript, defining its theme, direction, and framework. JY contributed to the conception and design of the manuscript. HW & BCW drafted the manuscript. LSL reviewed and revised the manuscript for language, grammatical structure, and logical coherence, collected relevant literature, and offered valuable suggestions for improving certain aspects of the manuscript. All authors reviewed and approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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