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REVIEW

PANoptosis: Cross-Talk Among Apoptosis, Necroptosis, and Pyroptosis in Neurological Disorders

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Abstract: Cell death mechanisms play a critical role in organismal development and homeostasis, primarily categorized into energy-dependent programmed cell death (PCD) and energy-independent necrotic cell death. PCD, regulated through various forms such as apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagic cell death, is essential for maintaining tissue stability and eliminating abnormal cells. Dysregulation of PCD is associated with numerous diseases, including cancer and neurodegenerative disorders. Recent studies have revealed extensive crosstalk and coordination among classical cell death pathways, leading to the identification of a novel programmed cell death mode termed PANoptosis. PANoptosis involves the dynamic assembly of the PANoptosome complex, which simultaneously activates apoptosis, pyroptosis, and necroptosis pathways in response to pathogen infection or tissue damage. In neurological diseases, PANoptosis exhibits dual roles: it can eliminate pathogen-infected cells but may also exacerbate neuroinflammation and neuronal death, contributing to the progression of neurodegenerative disorders. This review critically evaluates the molecular mechanisms of PANoptosis, its dual roles in neurological diseases (eg, Alzheimer's disease, Parkinson's disease, stroke, and glioma), and potential therapeutic strategies targeting PANoptosis, including small-molecule inhibitors, genome editing, and delivery technologies. By addressing conflicting evidence and outstanding questions, this review aims to provide a comprehensive framework for future research and clinical applications. Future research should focus on elucidating the molecular regulatory networks of PANoptosis, developing specific inhibitors, and advancing clinical applications to provide novel insights into the precise treatment of neurological diseases.

Keywords: PANoptosis, neurodegenerative diseases, PANoptosome, inflammasomes, neuroprotection

Introduction

Traditionally, cell death mechanisms are divided into two types: energy - requiring programmed cell death (PCD) and energy - independent necrotic cell death.[1,2] Cell death is crucial for organismal development and homeostasis.[3] Cell death is crucial for development and homeostasis. During development, it's essential to remove extra cells for normal morphogenesis and organ formation.[4] In adulthood, it's vital to clear self - reactive immune cells, cancer cells, and damaged cells to maintain internal balance. Too much or too little cell death in the body can lead to human diseases.[5] In neurodegenerative diseases, neurons that should survive to maintain nerve function die.[6] In cancer, cells that should be eliminated with cancer - causing mutations are not removed.[7] Programmed Cell Death (PCD) is a gene - controlled, orderly cell death process.[8] It's crucial for multicellular organism development, tissue stability maintenance, and removal of abnormal cells.[2] Key forms of PCD are apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagic cell death, involving different signaling pathways and regulatory mechanisms, such as the extrinsic death receptor and intrinsic mitochondrial pathways.[9] PCD is active throughout an organism's life: in embryonic development, it regulates cell numbers; in the immune system, it clears infected cells.[10]

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Table 1 Targeting PANoptosis: Therapeutic Strategies

Inhibitors	Associated Diseases	Mode of Action	Targets	References
MCC950	AD, Ischemic Stroke	Inhibits NLRP3 inflammasome assembly and activation, reducing IL-1β release and neuroinflammation	NLRP3 inflammasome	[69–72]
OLT1177	ICH	Inhibits NLRP3 inflammasome activation and IL-1β release	NLRP3 inflammasome	[73]
CY-09	Depression	Directly binds to NLRP3, blocking its ATPase activity and inflammasome activation	NLRP3 inflammasome	[74]
Tranilast	Stroke	Suppresses NLRP3 inflammasome activation and reduces neuroinflammation	NLRP3 inflammasome	[75]
Emricasan	Zika virus infection	irreversible pan-caspase inhibitor, blocks Caspase-3, −8, and −9 activation	Caspase family	[76]
Q-VD-OPh	Stroke	Broad-spectrum caspase inhibitor, reduces neuronal death and infarct volume	Caspase-1, −3, −8, −9	[77]

Abnormal PCD regulation is associated with various diseases, including cancer, neurodegenerative, cardiovascular, and metabolic diseases (Table 1).[11] Therefore, studying PCD mechanisms and regulation is key to understanding life processes and developing disease treatment strategies.[12]

Classic cell death patterns like apoptosis, pyroptosis, and necroptosis were long considered independent pathways.[13] However, recent studies have shown extensive crosstalk and coordination among these pathways.[12] In nervous system diseases, apoptotic, pyroptotic, and necroptotic pathways interact via shared molecules like Caspase-8 and RIPK1, and upstream sensors like ZBP1.[14] This forms a new programmed cell death pattern called PANoptosis. It was first proposed by Malireddi et al in 2019.[15] Panoptosis occurs when cells assemble a PANoptosome complex in response to pathogen infection or tissue damage.[16] This complex activates multiple death pathways, triggering an irreversible inflammatory cascade. This complex forms through the involvement of key molecules in pyroptosis, apoptosis, and necroptosis. It also involves epigenetic regulators like HMGB1. These regulators amplify inflammatory signals, creating a positive feedback loop.[17]

The nervous system is vulnerable to PANoptosis due to its limited regenerative capacity and high energy demands.[18] In neurodegenerative diseases like Alzheimer's and Parkinson's, panoptosis activation causes neuron death and worsens inflammation.[19] In Alzheimer's disease, β-amyloid oligomers activate ZBP1-PANoptosome in microglia, causing neuronal mitochondrial ROS bursts and tau hyperphosphorylation, accelerating synapse loss.[20] In Parkinson's disease, α-synuclein fibrils activate the NLRP3/ASC axis to trigger PANoptosis in dopaminergic neurons, inducing a cascade that promotes substantia nigra pars compacta neuron degeneration.[21] In strokes, ischemic injury can trigger the RIPK3-MLKL pathway through mTOR-ULK1 autophagy imbalance, worsening blood-brain barrier leakage and neuroinflammation.[22]

Although PANoptosis mainly has pathological effects in neurological diseases, it can also be protective in some cases. For example, in neural infections, it can remove pathogen - infected cells. This limits pathogen spread. This dual nature highlights the need for precise regulation of PANoptosis.[23]

This review aims to critically evaluate the molecular mechanisms of PANoptosis, its dual roles in nervous system diseases (clearing pathogens vs driving neurodegeneration), and propose targeted intervention strategies. By addressing conflicting evidence and outstanding questions, this review seeks to provide a comprehensive framework for balancing its dual effects and designing multi-modal interventions for precise neuroprotection.

Molecular Mechanisms of Panoptosis

Dynamic Assembly of the PANoptosome Core Complex

The hub of panoptosis is the multi - signal - adapting platform PANoptosome, whose structure varies depending on the type of stimulus.[24] In infection models, after ZBP1 recognizes viral nucleic acids (such as influenza virus), it recruits RIPK3, Caspase - 8, and ASC to form the "ZBP1 - PANoptosome", which activates Caspase - 3, MLKL, and GSDMD, simultaneously driving three death pathways.[25] Specifically, ZBP1 recognizes viral nucleic acids through its Zαβ domain, forming liquid - liquid phase - separated condensates. It further binds to RIPK1 and RIPK3 through its RHIM domain to

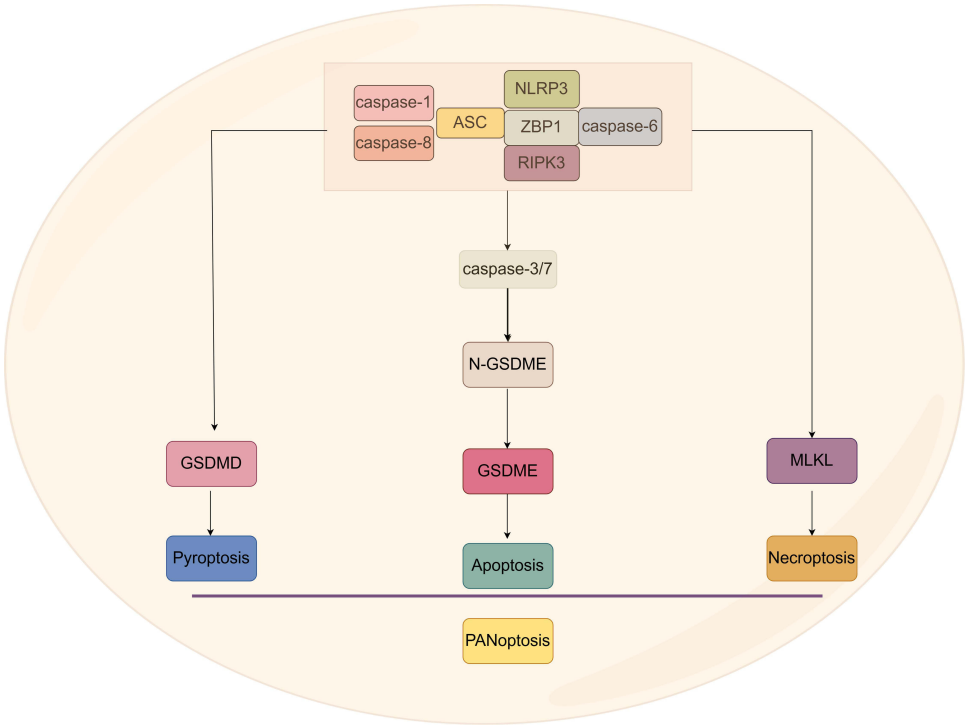

Figure 1 Molecular Mechanisms of PANoptosome Assembly and Activation in Infection and Neurodegenerative Models.

assemble the PANoptosome complex. This process not only activates the Caspase - 3 - mediated apoptotic pathway but also, through the activation of MLKL and GSDMD, mediates necroptosis and pyroptosis, respectively (Figure 1).[16]

In neurodegenerative models, Aβ/Tau activates the NLRP3 inflammasome, promoting ASC oligomerization and recruiting Pro - Caspase - 1 and Caspase - 8 to form the "NLRP3 - PANoptosome", leading to IL - 1β release and mitochondrial apoptosis. The activation of the NLRP3 inflammasome is a key step in the inflammatory response in neurodegenerative diseases. By recruiting ASC and Pro - Caspase - 1, it forms the inflammasome complex, which then activates Caspase - 1, promoting the maturation and release of IL - 1β.[26] Meanwhile, the recruitment and activation of Caspase - 8 further mediate the mitochondrial apoptotic pathway, resulting in neuronal death.

Key Molecular Interactions

Caspase - 8 has a dual function of cleaving GSDMD (pyroptosis) and activating Caspase - 3 (apoptosis).[27] Under TNFα stimulation, RIPK1 promotes necroptosis through its kinase activity or recruits FADD - Caspase - 8 to trigger apoptosis through its scaffolding function.[28] Caspase - 8 can directly cleave GSDMD, causing the release of the N - terminal fragment of GSDMD, which inserts into the cell membrane to form pores, thereby triggering pyroptosis.[27] In addition, Caspase - 8 can also activate Caspase - 3, which further cleaves substrates such as GSDME, leading to apoptosis.[29]

Under TNFα stimulation, RIPK1 can drive necroptosis via its kinase activity. When TNFα binds to TNFR1, RIPK1 moves to complex I, activates NF-κB signaling, and boosts anti-apoptotic gene expression.[30] When certain conditions arise, RIPK1 can move to complex II, bind to FADD and Caspase-8, and activate Caspase-8, triggering apoptosis. Additionally, RIPK1 can bind to RIPK3, activate MLKL, and induce necroptosis.[31] The Interactions and regulatory mechanisms of key molecules reveal the complexity of programmed cell death. They also offer potential targets for developing new therapeutic strategies.

The Role of PANoptosis in Neurological Disorders

Alzheimer's Disease (AD)

AD is a common neurodegenerative disease mainly affecting the elderly.[32] It is characterized by memory loss, cognitive decline, and changes in behavior and personality, significantly impacting patients' quality of life.[33] The pathological

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features of AD include the deposition of beta - amyloid (Aβ) plaques and the excessive phosphorylation of tau protein, forming neurofibrillary tangles in the brain. These changes lead to neuronal damage and death.[34]

In AD, Aβ-induced PANoptosis is a complex process involving multiple molecular mechanisms. Specifically, Aβ oligomers can activate TLR4 on neuron membranes, triggering MyD88-dependent NLRP3 inflammasome assembly and IL-1β release, a marker of pyroptosis.[20] Concurrently, Caspase-8 induces mitochondrial apoptosis by cleaving Bid protein.[20] Clinical evidence shows that in AD patients, the level of GSDMD-NT fragments (pyroptosis markers) in cerebrospinal fluid correlates positively with phosphorylated Tau protein levels. This suggests a link between PANoptosis activation and AD pathology.[35] However, conflicting evidence exists regarding the precise role of PANoptosis in AD progression, particularly in the context of Aβ clearance versus neuroinflammation exacerbation. Further research is needed to clarify these mechanisms.

The NLRP3 inflammasome plays a key role in PANoptosis. When activated, it causes the maturation and secretion of IL - 1β and IL - 18. Also, by promoting inflammation and cell death, it worsens AD neuroinflammation.[36] Aβ and Tau can be taken up by microglia.[37] They destabilize lysosomes and release cathepsin B.[38] This process activates the NLRP3 inflammasome. It boosts IL - 1β secretion, thus worsening the disease.[39] Recent studies have made significant progress in developing NLRP3 inflammasome inhibitors. These inhibitors, including MCC950, CY-09, OLT1177, Tranilast, and Oridonin, can directly or indirectly inhibit the activation of the NLRP3 inflammasome. This inhibition reduces inflammation and cell death, thereby improving cognitive function in AD patients.[40] Additionally, Some traditional Chinese medicine extracts, such as silybin, Lycium polysaccharide, and glycyrrhizin, can lower the protein and mRNA levels of NLRP3, IL-1β, and IL-18. This reduces neuronal damage and improves cognitive function.[41]

In summary, PANoptosis in AD involves complex mechanisms with cross-regulation of multiple molecules and signaling pathways. Intervening in NLRP3 inflammasome activation and expression can suppress central neuroinflammation, enhance Aβ clearance, and improve cognitive dysfunction. These findings offer a theoretical basis and potential targets for new therapies.

Parkinson's Disease (PD)

PD is a common neurodegenerative disorder that mainly affects middle-aged and elderly people.[42] It is characterized by movement problems such as tremors, stiffness, slow movement, and balance difficulties.[43] The pathological features of PD include the significant loss of dopaminergic neurons in the substantia nigra of the midbrain and the formation of Lewy bodies, which are primarily composed of aggregated alpha-synuclein.[44]

In PD, PANoptosis, a complex cell death form involving pyroptosis, apoptosis, and necroptosis, has gained attention for its mechanisms. One key pathological feature of PD is the abnormal aggregation of α-synuclein (α-Syn). These aggregates cause mitochondrial ROS bursts, activating the RIPK1/Caspase-8 axis and promoting dopaminergic neuron death.[45] In addition, the abnormal aggregation of α-Syn can spread between neurons via a prion-like mechanism, causing more neuronal damage and death. This process involves the release, internalization, and misfolding of α-Syn, propagating pathological changes between neurons.[46] The PANoptosome assembly involves multiple proteins, including ZBP1, RIPK1, RIPK3, CASP8, and FADD. These proteins interact to form a multimeric complex, starting the PANoptosis process. In animal models, the RIPK1 inhibitor Nec-1s significantly improves motor dysfunction in MPTP-induced mouse models of PD, showing potential therapeutic value.[47] However, the precise role of PANoptosis in PD progression remains controversial, particularly in the context of α-Syn propagation and neuroinflammation. Further studies are needed to address these gaps.

Ischemic Stroke

Ischemic stroke, a common cerebrovascular disease, is caused by blocked or severely narrowed brain blood vessels.[48] This reduces cerebral blood flow, leading to brain tissue ischemia, hypoxia, and death.[49] It has high incidence, prevalence, recurrence, disability, and mortality rates.[50]

In ischemic stroke, the inflammatory storm during reperfusion is a key pathological process. In the MCAO model, 1 hour of ischemia significantly increases RIPK3 phosphorylation, inducing necroptosis.[51] At 24 hours post - reperfusion, Caspase - 1 activation triggers pyroptosis in microglia, further disrupting the blood - brain barrier.[52] During this process, PANoptosis is triggered. It causes massive neuronal and microglial death, worsening brain tissue damage.[53] PANoptosis,

which encompasses pyroptosis, apoptosis, and necroptosis, plays a key role in ischemic stroke pathophysiology. Researching PANoptosis mechanisms in ischemic stroke can aid new therapy development. This can reduce reperfusion injury and enhance patient recovery. However, the dual role of PANoptosis in ischemic stroke, particularly its protective versus detrimental effects, remains unclear and warrants further investigation.

Hemorrhagic Stroke

Hemorrhagic stroke, an acute cerebrovascular disease caused by cerebral vessel rupture, has high mortality and disability rates.[54] It often suddenly occurs during activity, manifesting as headache, nausea, vomiting, impaired consciousness, and limb paralysis.[49] Depending on the bleeding site, it is mainly divided into intracerebral hemorrhage and subarachnoid hemorrhage.[55]

In hemorrhagic stroke, free hemin upregulates HMGB1 via TLR4, triggering microglial PANoptosis and releasing IL-18, which worsens brain edema.[56] This process is crucial in the pathophysiology of hemorrhagic stroke. Studies show that after brain hemorrhage, erythrocyte components like hemoglobin and its degradation products (heme and iron) are released.[57] The degraded iron ions induce lipid peroxidation, producing free radicals that damage the blood-brain barrier and worsen cerebral edema.[58] In addition, TLR4 signaling activation is closely related to neuron apoptosis, and modulating this pathway can mediate neuron apoptosis.[59] Studying PANoptosis mechanisms in hemorrhagic stroke can help develop new treatments to reduce brain edema and neuron damage, improving patient outcomes. However, the precise mechanisms underlying PANoptosis in hemorrhagic stroke remain poorly understood, and further research is needed to clarify its role in disease progression.

Glioma

Gliomas, the most common primary tumors in the central nervous system, originate from neural glial cells (such as astrocytes and oligodendrocytes), accounting for about 30% of all brain tumors.[60] According to the WHO grading system, gliomas can be classified into grades I - IV, with glioblastoma (GBM, grade IV) being the most malignant, highly invasive, and prone to recurrence, having a median survival period of only 12–18 months.[61] Currently, standard treatments for gliomas mainly include surgical resection combined with radiochemotherapy (eg, temozolomide). However, these treatments often face challenges such as drug resistance and difficulty penetrating the blood-brain barrier.[62]

Panoptosis, by regulating the cleavage of Caspase family proteins (such as CASP1/3/8) and Gasdermin proteins (such as GSDMD), plays multiple roles in gliomas.[63] GPX8-mediated panoptosis drives microglia to tumors, releases DAMPs, and boosts tumor immunogenicity. It also reshapes the immune microenvironment by increasing T-cell infiltration and activating dendritic cells, improving the response to immune therapies like PD-1/PD-L1 inhibitors.[64] Panoptosis-related genes (eg, ZBP1, NLRP3) are linked to glioma prognosis. They can guide personalized treatments, such as predicting temozolomide resistance or radiotherapy sensitivity.[65]

Targeting panoptosis (eg, disrupting PANoptosome assembly or Gasdermin function) can reverse chemotherapy resistance in high-grade gliomas.[66] It also works with oncolytic viruses and CAR-T therapy to enhance antitumor immune responses. This approach offers new ways to develop low-toxicity drugs and improve combination therapies.[67] However, the dual role of PANoptosis in glioma progression, particularly its impact on tumor immunogenicity versus tumor cell survival, remains controversial. Future research should focus on clarifying these mechanisms to optimize therapeutic strategies.

Targeting PANoptosis: Therapeutic Strategies

Small Molecule Inhibitor Development

NLRP3 Inhibitors

NLRP3 inhibitors are compounds designed to target the NLRP3 inflammasome, a critical component of the innate immune system involved in detecting microbial infections and cellular damage. By suppressing NLRP3, these compounds can modulate inflammatory responses, prevent tissue damage, and reduce the release of pro-inflammatory cytokines (eg, IL-1β and IL-18), as well as limit inflammatory necrosis.[68]

NLRP3 inhibitors show significant therapeutic potential in neurological diseases. In AD models, like APP/PS1 mice, the NLRP3 inhibitor MCC950 demonstrates remarkable therapeutic effects.[69] For example, intraperitoneal injection of 10 mg / kg MCC950 daily reduces Aβ plaques by 50% and significantly improves cognitive function in APP/PS1 mice. This may be due to MCC950's direct inhibition of the NLRP3 inflammasome, reducing inflammation and neuronal damage. Additionally, MCC950 promotes non - inflammatory Aβ clearance, further improving cognitive function.[70]

Besides Alzheimer's, NLRP3 inhibitors show promise in other neurological diseases. In ischemia - reperfusion models, MCC950 significantly reduces brain injury and improves neurologic function post - ischemic stroke.[71] Additionally, MCC950 exerts neuroprotective effects by modulating intracellular calcium signaling pathways and autophagy.[72]

Developing NLRP3 inhibitors with novel structures and mechanisms is a hot research area. For instance, Sorbremnoids A and B, found in the fungus Penicillium citrinum, are new NLRP3 inhibitors. They directly target the NLRP3 protein, inhibiting NLRP3 inflammasome assembly and activation, and show potential for treating inflammatory and neurodegenerative diseases. These compounds have significant anti - inflammatory activity in diabetic wound healing models, accelerating healing and suggesting clinical potential.[26]

In addition, other NLRP3 inhibitors, such as CY-09, OLT1177, Tranilast, and Oridonin, have shown therapeutic potential in various neurological disease models.[73–75] These inhibitors exert neuroprotective effects by directly or indirectly inhibiting NLRP3 inflammasome activation, reducing inflammation and cell death.

In summary, NLRP3 inhibitors like MCC950 show significant therapeutic potential in various neurological diseases by inhibiting the NLRP3 inflammasome and reducing neuroinflammation. The ongoing development of new NLRP3 inhibitors with improved efficacy and safety may offer novel treatment options for patients with neurological diseases.

Broad-Spectrum Apoptosis Inhibitors

Broad - spectrum apoptosis inhibitors are substances that can block multiple apoptosis pathways by targeting key apoptotic signaling molecules, thus protecting cells from programmed death.[78] These compounds show potential therapeutic value in various disease models, especially in neurodegenerative and cardiovascular diseases.

Broad - spectrum apoptosis inhibitors have promising therapeutic effects in neurological diseases. Emricasan (IDN - 6556), an irreversible pan - caspase inhibitor, targets key apoptotic effector proteins like caspase - 3, - 8, and - 9, reducing neuronal apoptosis.[76] In vitro studies show Emricasan has neuroprotective effects in astrocyte models and blocks caspase-3 activation caused by Zika virus.[79]

Other broad - spectrum apoptosis inhibitors, like Q - VD - OPh and Z - VAD - FMK, have also been widely studied. Q - VD - OPh inhibits caspase - 1, - 3, - 8, and - 9 activities, reducing neuronal death and infarct volume in stroke models.[77] Z-VAD-FMK, on the other hand, blocks the pan-caspase pathway to inhibit Iron-overloaded rats, which is a form of axonal degeneration.[80] These drugs work by inhibiting mitochondrial apoptosis and death receptor pathways. They also regulate inflammasome activation (eg, NLRP3) and reduce pro - inflammatory cytokine release, such as IL - 1β. This dual action helps alleviate neuroinflammation and glial activation.

Future research must tackle key challenges like enhancing blood - brain - barrier penetration with optimized drug delivery systems (eg, nanoparticles or exosomes) and developing precise biomarkers to identify optimal treatment windows. Also, chronic apoptosis inhibition might disrupt physiological cell clearance and increase cancer risk, so careful evaluation is needed in clinical translation.

Genome Editing and Delivery Technologies

Genome editing tech like CRISPR - Cas9 enables precise genome modifications. CRISPR - Cas9 comprises a Cas9 nuclease and an sgRNA, which identifies and binds specific DNA sequences, induces double - strand breaks, and allows gene editing. Delivery tech is essential for introducing genome editing tools or therapeutic genes into cells, with common methods including viral and non - viral vectors.[81]

PANoptosis-targeting genome editing and delivery technologies have shown remarkable potential in treating neurological disorders. For example, CRISPR/Cas9 has achieved groundbreaking progress in Huntington's disease (HD) treatment. In HD pig models, adeno-associated virus (AAV)-delivered CRISPR/Cas9 systems successfully targeted the CAG repeat expansion region in the mutant Huntington gene (HTT) and replaced it with normal sequences. This

intervention significantly reduced mutant protein neurotoxicity and improved motor deficits.[82] Similar applications are being explored in Alzheimer's and Parkinson's diseases, such as targeting the APP or α-synuclein genes to reduce pathological protein aggregation.[83]

CRISPR interference (CRISPRi), which uses a catalytically inactive Cas9 (dCas9) to inhibit specific gene transcription, offers a novel strategy for modulating neuroinflammation or apoptosis-related pathways.

In neurological gene therapy, viral vectors (eg, AAV) are the top choice due to their efficient blood - brain - barrier penetration and long - term expression. For instance, AAV9 vectors successfully delivered CRISPR components to the brain and achieved precise editing in HD pig models via intracranial or intravenous injection.[84] Non - viral delivery systems, like liposomes and exosomes, are also being studied. They have advantages such as low immunogenicity and repeatable administration. However, research is still focused on improving their targeting efficiency and delivery accuracy.

Future research should focus on developing more precise delivery methods, like targeting specific neuron subtypes, and combination therapies, such as combining genome editing with neurotrophic factor delivery, to improve treatment effectiveness and minimize off-target effects. However, long-term safety issues, including immune reactions and cancer-related risks, need careful assessment through large-scale preclinical studies.

Challenges and Future Directions

Research on PANoptosis faces challenges in understanding its complex molecular mechanisms, developing specific inhibitors, and advancing clinical applications. However, ongoing research and technological progress are increasingly revealing its therapeutic potential. Future research should focus on a deeper understanding of PANoptosis molecular mechanisms, particularly the assembly and regulation of PANoptosomes, which could pave the way for the identification of more specific therapeutic targets. Additionally, the development of novel inhibitors targeting PANoptosome sensors and other components of the PANoptosis pathway may yield improved therapeutic outcomes.

Furthermore, using multi-omics technologies to analyze PANoptosis regulatory networks can reveal new molecular targets and biomarkers. Another key direction is advancing clinical trials for PANoptosis-related drugs, particularly for neurodegenerative diseases and cancer. Nanomedicine has great potential in developing new tumor-targeted PANoptosis-inducing agents. Also, integrative approaches, like combining traditional Chinese and Western medicine or applying photodynamic therapy, open up new avenues for PANoptosis research.

In summary, PANoptosis research holds significant promise in elucidating molecular mechanisms, advancing drug development, and expanding clinical applications. Future progress in PANoptosis research should be driven by interdisciplinary collaboration, multi-omics technologies, nanomedicine, and integrative therapies. However, addressing conflicting evidence and outstanding questions, particularly regarding the dual roles of PANoptosis in disease progression, remains a critical challenge that requires further investigation.

Disclosure

The authors declare that they have no competing interests.

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