

Molecular Pathways of Neuronal Apoptosis in Neurodegenerative Diseases and Intervention Strategies

Jingyang Bu*

Hong Kong University of Science and Technology, Hong Kong, China

Abstract. Neurodegenerative diseases are a group of progressive conditions characterized by the dysfunction and death of neurons, leading to cognitive and motor impairments. A key process in the pathogenesis of these diseases is neuronal apoptosis, which is regulated by a complex array of molecular pathways. This paper provides an overview of the intrinsic and extrinsic apoptotic pathways, highlighting the critical role of caspases in executing cell death. It also discusses additional pathways, such as endoplasmic reticulum stress, DNA damage response, and autophagy, which contribute to the initiation and progression of neuronal apoptosis in neurodegenerative diseases.

1 Introduction

1.1 Definition of Neurodegenerative Diseases

Neurodegenerative diseases are a group of debilitating disorders characterized by the progressive loss of structure and function of neurons, leading to a decline in cognitive and motor abilities. These diseases are typically associated with aging, although some forms can affect individuals at any age. The term "neurodegenerative" encompasses a range of conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis (ALS), and various forms of dementia. The defining feature of these diseases is the gradual degeneration and death of neurons, which can be attributed to a complex interplay of genetic, environmental, and lifestyle factors.

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, are a group of progressive disorders characterized by the gradual loss of neurons, leading to cognitive decline, motor dysfunction, and other debilitating symptoms. A central process in the pathogenesis of these diseases is neuronal apoptosis—programmed cell death. In Alzheimer's disease, for example, the accumulation of amyloid-beta plaques triggers neuronal apoptosis, contributing to memory loss and cognitive impairment. Similarly, in Parkinson's disease, the loss of dopaminergic neurons in the substantia nigra is partly driven by apoptotic mechanisms, leading to motor deficits. Huntington's disease, caused by a genetic mutation, is marked by the premature death of neurons, especially in the basal ganglia, where apoptosis plays a crucial role in disease progression.

The impact of neurodegenerative diseases is profound, affecting not only the individuals diagnosed but also their

families and caregivers. As the population ages, the prevalence of these conditions is expected to increase, placing a significant burden on healthcare systems worldwide. Despite the significant societal impact, the molecular mechanisms underlying neurodegeneration are not fully understood, and there are currently no cures for these diseases. However, research has made strides in identifying the key molecular pathways involved in neuronal apoptosis, which is the programmed cell death process contributing to the neuronal loss observed in neurodegenerative diseases.

Understanding the molecular pathways of neuronal apoptosis is crucial for developing effective intervention strategies. This paper aims to provide an overview of the molecular mechanisms involved in neuronal apoptosis in neurodegenerative diseases and to discuss potential intervention strategies that target these pathways. By elucidating the complex processes that lead to neuronal death, we hope to contribute to developing novel therapeutic approaches that can slow or halt the progression of these devastating diseases.

1.2 Importance of Understanding Neuronal Apoptosis

Understanding neuronal apoptosis is pivotal for advancing our knowledge of neurodegenerative diseases and for developing effective therapeutic interventions. Apoptosis, or programmed cell death, is a tightly regulated process that plays a crucial role in maintaining tissue homeostasis and eliminating damaged or unnecessary cells. In the context of neurodegenerative diseases, the dysregulation of apoptosis contributes to the progressive loss of neuronal function and structure, leading to the characteristic symptoms and eventual disability associated with these conditions.

*Email: 3800679351@qq.com

Caspases, a family of cysteine proteases, play a central role in executing neuronal apoptosis. In neurodegenerative diseases, caspases are key mediators of cell death, particularly caspase-3, -6, and -9, which are involved in the intrinsic and extrinsic pathways of apoptosis. Caspase-9 is a crucial initiator of caspase in the intrinsic pathway. It is activated by the apoptosome, a complex formed by cytochrome c and apoptotic protease activating factor-1 (Apaf-1). Caspase-9 then activates downstream executioner caspases, particularly caspase-3. In Alzheimer's disease, for example, mitochondrial dysfunction induced by amyloid-beta plaques can trigger the activation of caspase-9, initiating the apoptotic cascade and contributing to neuronal loss. Caspase-9 has also been implicated in Parkinson's disease, where it is activated following the loss of dopaminergic neurons in the substantia nigra, further accelerating the progression of motor deficits. Caspase-3 is the most well-known executioner caspase in the apoptosis process. Once activated, caspase-3 cleaves a wide range of substrates, including structural proteins and enzymes, leading to the characteristic morphological changes of apoptosis, such as DNA fragmentation and cell shrinkage. In both Alzheimer's and Huntington's diseases, caspase-3 activation is a hallmark of neurodegeneration. In Alzheimer's, for example, caspase-3 is activated by both the intrinsic mitochondrial pathway and the extrinsic pathway (through caspase-8 and Bid cleavage), leading to widespread neuronal death. Caspase-6 is another executioner caspase that has been implicated in neurodegenerative diseases, particularly in Huntington's disease. The mutation in the huntingtin protein that causes Huntington's disease leads to the accumulation of toxic protein aggregates that can activate caspase-6. Caspase-6 then cleaves substrates involved in neuronal structure and function, contributing to neuronal death and disease progression. Understanding the specific roles of these caspases in neurodegenerative diseases is crucial for developing targeted therapies. For example, inhibiting caspase-3 activity could prevent the execution of apoptosis in neurons, while inhibiting caspase-9 may prevent the initiation of apoptosis triggered by mitochondrial dysfunction. Similarly, targeting caspase-6 in diseases like Huntington's could help prevent the cellular damage caused by the mutant huntingtin protein.

The importance of studying neuronal apoptosis lies in its potential to reveal the underlying mechanisms that drive neurodegeneration. By dissecting the molecular pathways involved in the initiation and execution of apoptosis, researchers can identify key factors that, when targeted, may slow or halt the progression of neuronal death. This understanding is essential for the development of targeted therapies that can intervene in the disease process, potentially leading to improved outcomes for patients. Moreover, the study of neuronal apoptosis provides insights into the differential vulnerability of neurons within the brain. Different neuronal populations are affected to varying degrees in different neurodegenerative diseases, suggesting that specific cellular processes or genetic factors may render certain neurons more susceptible to apoptosis. Identifying these factors can help researchers develop a more nuanced

understanding of disease pathology and design therapies tailored to the specific needs of affected neuronal populations. Furthermore, understanding neuronal apoptosis is critical for the development of neuroprotective strategies.^[1]Neuroprotection aims to preserve the health and function of neurons, potentially slowing the progression of neurodegenerative diseases. By targeting the molecular pathways that lead to apoptosis, neuroprotective therapies may be able to prevent or mitigate neuronal loss, thereby preserving cognitive and motor function in patients.

In summary, the study of neuronal apoptosis is fundamental to our understanding of the pathogenesis of neurodegenerative diseases and crucial for developing novel therapeutic strategies. As research continues to uncover the complex interplay of molecular mechanisms involved in neuronal death, the hope is that this knowledge will translate into effective treatments that can improve the quality of life for those affected by these devastating conditions.^[2]

1.3 Objective of the Paper

This paper aims to delve into the molecular pathways that govern neuronal apoptosis in the context of neurodegenerative diseases and explore the intervention strategies that have been proposed or are under development to combat these processes.

The paper aims to provide a comprehensive overview of the current understanding of the molecular mechanisms that trigger and execute neuronal apoptosis, highlighting the key proteins, signaling pathways, and genetic factors that contribute to this phenomenon.^[3]Much of the paper will discuss the various intervention strategies targeting these molecular pathways. These strategies include pharmacological interventions, gene therapy, stem cell therapy, and lifestyle modifications. The goal is to evaluate the potential efficacy and challenges associated with each approach and identify the gaps in our current knowledge that need to be addressed to advance these therapies toward clinical application.^[4]

Furthermore, the paper seeks to underscore the importance of a multidisciplinary approach to research in this field. Neurodegenerative diseases are complex and involve many biological processes, necessitating collaboration between neuroscientists, molecular biologists, geneticists, and clinicians. By integrating insights from different disciplines, we can develop a more holistic understanding of neuronal apoptosis and design more effective treatment strategies.

This paper aims to contribute to the ongoing efforts in neurodegenerative disease research by synthesizing current knowledge and identifying areas that require further investigation. By presenting the latest findings and discussing the challenges and future directions in the study of neuronal apoptosis, we hope to inspire further research and stimulate the development of novel therapeutic approaches that can ultimately improve the prognosis and quality of life for patients suffering from these debilitating conditions.

2 Molecular Pathways of Neuronal Apoptosis

2.1 Intrinsic Pathway

The intrinsic pathway of neuronal apoptosis, also known as the mitochondrial pathway, is a critical process in neurodegenerative diseases. This pathway is initiated by various cellular stressors, including oxidative stress, DNA damage, and endoplasmic reticulum (ER) stress, which can disrupt the mitochondrial membrane potential and release pro-apoptotic factors such as cytochrome c. The release of cytochrome c into the cytosol is a pivotal event, as it triggers the formation of the apoptosome, a complex that includes apoptotic protease activating factor-1 (Apaf-1) and procaspase-9. Once the apoptosome is formed, it activates caspase-9, activating the caspase-3, -6, and -7 executioner caspases. These caspases are responsible for the biochemical and morphological changes associated with apoptosis, including DNA fragmentation, cell shrinkage, and the formation of apoptotic bodies.^[5] The Bcl-2 family of proteins tightly regulates the intrinsic pathway, which includes both pro-apoptotic members, such as Bax and Bak, and anti-apoptotic members, such as Bcl-2 and Bcl-xL. The balance between these opposing forces determines the susceptibility of neurons to apoptosis.

In neurodegenerative diseases, the intrinsic pathway is often dysregulated, with increased expression of pro-apoptotic proteins and decreased expression of anti-apoptotic proteins, leading to neuronal loss. For example, in Alzheimer's disease, the accumulation of amyloid-beta peptides can induce mitochondrial dysfunction and activate the intrinsic pathway, while in Parkinson's disease, the loss of protective factors such as DJ-1 and the accumulation of alpha-synuclein can also lead to mitochondrial dysfunction and apoptosis.

Understanding the molecular mechanisms of the intrinsic pathway is crucial for the development of therapeutic strategies aimed at preventing neuronal apoptosis. Targeting key components of this pathway, such as the Bcl-2 family proteins or the caspases, may provide a means to protect neurons from death and slow the progression of neurodegenerative diseases. Additionally, identifying the specific cellular stressors that activate the intrinsic pathway in different diseases can help develop disease-specific interventions that address the underlying causes of neuronal apoptosis.^[6]

2.2 Extrinsic Pathway

The extrinsic pathway of neuronal apoptosis is initiated by activating cell surface death receptors, which belong to the tumor necrosis factor (TNF) receptor superfamily. This pathway is a critical mechanism in the regulation of cell survival and death in the nervous system, and its dysregulation has been implicated in several neurodegenerative diseases. The extrinsic pathway is triggered by the binding of extracellular ligands, such as Fas ligand (FasL) or TNF-related apoptosis-inducing ligand (TRAIL), to their respective receptors, such as Fas

or death receptor 4 (DR4) and death receptor 5 (DR5). Upon ligand binding, the death receptors recruit and activate an adaptor protein, Fas-associated death domain (FADD), which recruits and activates initiator caspase-8. This activation leads to the formation of the death-inducing signaling complex (DISC), a platform that amplifies the apoptotic signal.^[7] The activation of caspase-8 is a critical checkpoint in the extrinsic pathway, as it can either directly activate the executioner caspases, such as caspase-3, or cleave the pro-apoptotic Bcl-2 family member, Bid, to its truncated form, tBid. This truncated form can then engage the intrinsic pathway by promoting the release of cytochrome c from mitochondria, thus linking the extrinsic and intrinsic pathways.

In neurodegenerative diseases, the extrinsic pathway may be activated by various factors, including inflammation, oxidative stress, and the accumulation of misfolded proteins. For instance, in multiple sclerosis, the immune system's attack on neuronal cells can lead to the upregulation of death receptors and the subsequent activation of apoptosis.^[8] Similarly, in Alzheimer's disease, the presence of amyloid-beta plaques can induce the expression of death receptors on neuronal cells, leading to their demise.

The extrinsic pathway offers several potential targets for therapeutic intervention. Inhibiting the ligand-receptor interaction, blocking the formation of DISC, or inhibiting the activity of caspase-8 could potentially prevent the initiation of apoptosis. Additionally, understanding the crosstalk between the extrinsic and intrinsic pathways can provide insights into developing strategies that target these pathways' convergence points, thereby offering a broader spectrum of neuroprotection. The exploration of these targets is an active area of research, with the goal of developing drugs that can modulate the extrinsic pathway to protect neurons from apoptosis in neurodegenerative diseases.

2.3 Other Pathways

Beyond the intrinsic and extrinsic pathways, neuronal apoptosis in neurodegenerative diseases can also be influenced by various other molecular pathways that contribute to the complex interplay of cellular processes leading to cell death. These alternative pathways include the endoplasmic reticulum (ER) stress response, the DNA damage response, and the dysregulation of autophagy. ER stress occurs when the protein-folding capacity of the ER is overwhelmed, leading to the accumulation of misfolded proteins. This stress activates the unfolded protein response (UPR), which aims to restore ER homeostasis.^[9] However, if the stress is prolonged or too severe, the UPR can trigger apoptosis. In neurodegenerative diseases like Alzheimer's and Parkinson's, the accumulation of misfolded proteins such as amyloid-beta and alpha-synuclein can lead to chronic ER stress, contributing to neuronal apoptosis.

The DNA damage response pathway is another route to apoptosis. Neurons are particularly susceptible to DNA damage due to their high metabolic rate and limited capacity for regeneration. When extensive DNA damage

or repair mechanisms are impaired, cells can undergo apoptosis. For example, in ataxia telangiectasia mutated (ATM) deficiency, neurons exhibit increased sensitivity to DNA damage-induced apoptosis, highlighting the importance of DNA repair mechanisms in neuronal survival. Autophagy is a cellular process that degrades and recycles damaged organelles and proteins. While autophagy can protect neurons by removing aggregated proteins, excessive or insufficient autophagy can lead to neuronal death. In diseases like Huntington's, mutations in the huntingtin protein can impair autophagy, leading to the accumulation of toxic protein aggregates and apoptosis.

These alternative pathways intersect with the intrinsic and extrinsic pathways, creating a complex signal network that regulates neuronal survival.^[10] Understanding these interactions is crucial for developing therapeutic strategies that simultaneously modulate multiple pathways. For instance, drugs that can alleviate ER stress or enhance DNA repair mechanisms may have neuroprotective effects. Similarly, promoting a balanced autophagy process could help clear toxic protein aggregates and prevent apoptosis. The exploration of these pathways as potential therapeutic targets is an emerging area of research in neurodegenerative diseases, offering new avenues for developing treatments that can address the multifaceted nature of neuronal apoptosis.^[11]

While the intrinsic and extrinsic apoptotic pathways are often discussed separately in neurodegenerative diseases, they are frequently interconnected, amplifying the process of neuronal death. The intrinsic pathway, initiated by mitochondrial dysfunction and cellular stressors such as oxidative stress, DNA damage, and endoplasmic reticulum (ER) stress, can interact with the extrinsic pathway, particularly through the activation of pro-apoptotic members of the Bcl-2 family like Bid. Bid, once cleaved by caspase-8 in the extrinsic pathway, can translocate to the mitochondria, promoting the release of cytochrome c and further enhancing the apoptotic cascade via the intrinsic pathway.

Additionally, the DNA damage response and ER stress pathways are often triggered by similar insults, such as oxidative stress or protein misfolding. In neurodegenerative diseases like Alzheimer's and Parkinson's, the accumulation of misfolded proteins (e.g., amyloid-beta in Alzheimer's and alpha-synuclein in Parkinson's) can lead to chronic ER stress, which in turn activates the unfolded protein response (UPR). If unresolved, this stress can trigger apoptosis, further exacerbating neuronal loss. Interestingly, the UPR can also interact with the intrinsic apoptotic pathway, as prolonged ER stress can induce mitochondrial dysfunction, linking these two apoptotic routes. Autophagy, a process responsible for degrading damaged proteins and organelles, also interacts with apoptosis. In neurodegenerative diseases, impaired autophagic activity can lead to the accumulation of toxic protein aggregates, which can trigger ER stress and mitochondrial dysfunction, thus activating both the intrinsic and extrinsic apoptotic pathways. Moreover, excessive autophagy can lead to neuronal death, suggesting a delicate balance in maintaining cellular homeostasis. Together, these pathways create a complex network of signals that drive

neuronal apoptosis in neurodegenerative diseases. The crosstalk between these pathways—whether through direct molecular interactions or shared cellular stress responses—compounds the damage to neurons, making the process of neurodegeneration more aggressive and difficult to halt. Understanding these interactions is crucial for developing comprehensive therapeutic strategies that simultaneously target multiple pathways.

3 Intervention Strategies

Targeting caspases represents a central strategy in the intervention of neuronal apoptosis in neurodegenerative diseases. Caspases are a family of cysteine proteases that play a critical role in the execution phase of apoptosis. They exist as inactive precursors and are activated through a cascade of proteolytic events, leading to the cleavage of various cellular substrates and cell death. The caspase family can be divided into initiator caspases (such as caspase-8 and -9) and executioner caspases (such as caspase-3, -6, and -7). Inhibiting caspase activity has been a focal point for therapeutic intervention. One approach involves the use of small molecule inhibitors that can block the active site of caspases, thereby preventing their cleavage of substrates. For example, compounds like Z-VAD-FMK and Q-VD-OPh have been used in preclinical studies to inhibit caspase activity and protect neurons from apoptosis induced by various insults.

Another strategy is the development of dominant-negative mutants of caspases, which can competitively inhibit the activity of endogenous caspases by forming non-functional complexes. These mutants have been used in cellular and animal models to study the role of caspases in neurodegenerative processes and to assess their potential as therapeutic agents. Gene therapy approaches that target caspase expression or activity are also being explored. This includes the use of antisense oligonucleotides or small interfering RNA (siRNA) to reduce the levels of caspase proteins or the delivery of genes encoding for caspase inhibitors.

However, the targeting of caspases in neurodegenerative diseases is not without challenges. Caspases have essential roles in immune responses and development, and broad inhibition may lead to unintended side effects. Therefore, the development of selective caspase inhibitors that can specifically target the apoptotic caspases involved in neurodegeneration without affecting the physiological functions of other caspases is crucial. Additionally, the delivery of these therapeutics to the central nervous system poses a significant challenge due to the blood-brain barrier. Overcoming these hurdles will require innovative drug delivery strategies and a deep understanding of the caspase-dependent pathways in neurodegenerative diseases. Despite these challenges, the targeting of caspases remains a promising avenue for the development of neuroprotective therapies.

4 Conclusions

In conclusion, the intricate molecular pathways that govern neuronal apoptosis in neurodegenerative diseases

are a focal point for research aimed at developing therapeutic interventions. The intrinsic and extrinsic pathways, along with other cellular processes such as ER stress, DNA damage response, and autophagy, contribute to the complex interplay of signals that lead to neuronal cell death. Understanding these pathways has been crucial for identifying potential targets for intervention, such as the caspase family of proteins, which play a central role in executing apoptosis.

The development of intervention strategies has been challenging due to the complexity of neurodegenerative diseases and the multitude of factors that contribute to neuronal apoptosis. However, the pursuit of targeted therapies, such as caspase inhibitors, has shown promise in preclinical studies. These findings underscore the potential for pharmacological, genetic, and lifestyle interventions to modulate the molecular pathways involved in neuronal apoptosis, offering hope for the development of neuroprotective treatments.

Despite the progress made, there is still much to learn about the precise mechanisms that drive neuronal apoptosis in different neurodegenerative conditions. Future research should continue to explore the crosstalk between the various molecular pathways and identify disease-specific therapeutic targets. Additionally, efforts should be directed toward improving drug delivery across the blood-brain barrier and developing strategies that selectively target pathological processes without disrupting essential physiological functions.

Ultimately, the goal is to translate the growing knowledge about neuronal apoptosis into effective treatments that can slow or halt the progression of neurodegenerative diseases. This will require a concerted effort from researchers, clinicians, and pharmaceutical companies, as well as the support of patients and their families. By working together, we can move closer to a future where the devastating impact of neurodegenerative diseases is significantly reduced, and those affected can enjoy a better quality of life.

Reference

1. Mengqi Hao, Jianjian Chu, Tinglin Zhang, et al. Nanomaterials-mediated lysosomal regulation: a robust protein-clearance approach for the treatment of Alzheimer's disease[J].*Neural Regeneration Research*,2025,20(02):424-439.DOI:10.4103/NRR.NRR-D-23-01736.
2. Zhengyu An, Aidi Jiang, Jingqi Chen. Toward understanding the role of genomic repeat elements in neurodegenerative diseases[J].*Neural Regeneration Research*,2025,20(03):646-659.DOI:10.4103/NRR.NRR-D-23-01568.
3. Yanxi Li, Jing Xue, Yuejia Ma, et al. The complex roles of m6A modifications in neural stem cell proliferation, differentiation, and self-renewal and implications for memory and neurodegenerative diseases[J].*Neural Regeneration Research*,2025,20(06):1582-1598.DOI:10.4103/NRR.NRR-D-23-01872.
4. Hui Yang, Nan Mo, Le Tong, et al. Microglia lactylation in relation to central nervous system diseases[J].*Neural Regeneration Research*,2025,20(01):29-40.DOI:10.4103/NRR.NRR-D-23-00805.
5. Kedong Zhu, Hualong Wang, Keqiang Ye, et al. Netrin-1 signaling pathway mechanisms in neurodegenerative diseases[J].*Neural Regeneration Research*,2025,20(04):960-972.DOI:10.4103/NRR.NRR-D-23-01573.
6. Zhiyuan Yin, Jiahui Kang, Xuan Cheng. Investigating Müller glia reprogramming in mice: a retrospective of the last decade, and a look to the future[J].*Neural Regeneration Research*,2025,20(04):946-959.DOI:10.4103/NRR.NRR-D-23-01612.
7. Alessio Canovai, Pete A. Williams. Pyrroloquinoline quinone: a potential neuroprotective compound for neurodegenerative diseases targeting metabolism[J].*Neural Regeneration Research*,2025,20(01):41-53.DOI:10.4103/NRR.NRR-D-23-01921.
8. Qinchao Hu, Si Wang, Weiqi Zhang, et al. Unraveling brain aging through the lens of oral microbiota[J].*Neural Regeneration Research*,2025,20(07):1930-1943.DOI:10.4103/NRR.NRR-D-23-01761.
9. XiuYun Zhao, DeEn Xu, MingLei Wu, et al. Regulation and function of endoplasmic reticulum autophagy in neurodegenerative diseases[J].*Neural Regeneration Research*,2025,20(01):6-20.DOI:10.4103/NRR.NRR-D-23-00995.
10. Minghuang Gao, Xinyue Wang, Shijie Su, et al. Meningeal lymphatic vessel crosstalk with central nervous system immune cells in aging and neurodegenerative diseases[J].*Neural Regeneration Research*,2025,20(03):763-778.DOI:10.4103/NRR.NRR-D-23-01595.
11. Ikuko Maejima, Ken Sato. New aspects of a small GTPase RAB35 in brain development and function[J].*Neural Regeneration Research*,2025,20(07):1971-1980.DOI:10.4103/NRR.NRR-D-23-01543.